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(54) **MODULATION OF SIDE EFFECT PROFILE OF 5-ALPHA REDUCTASE INHIBITOR THERAPY**

(75) Inventors: **Om Dhingra**, Morrisville, NC (US); **James Bernstein**, Raleigh, NC (US)

(73) Assignee: **SOV Therapeutics**, Morrisville, NC (US)

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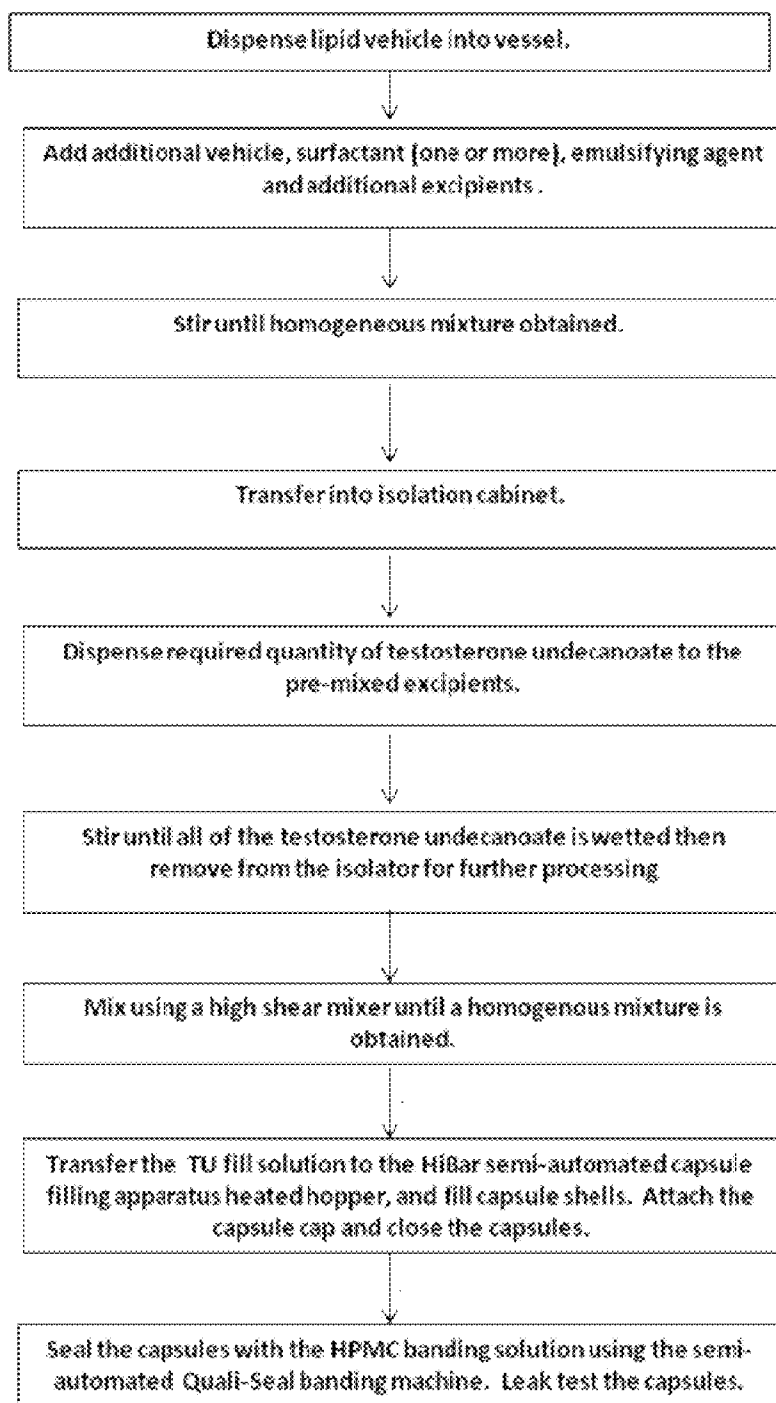
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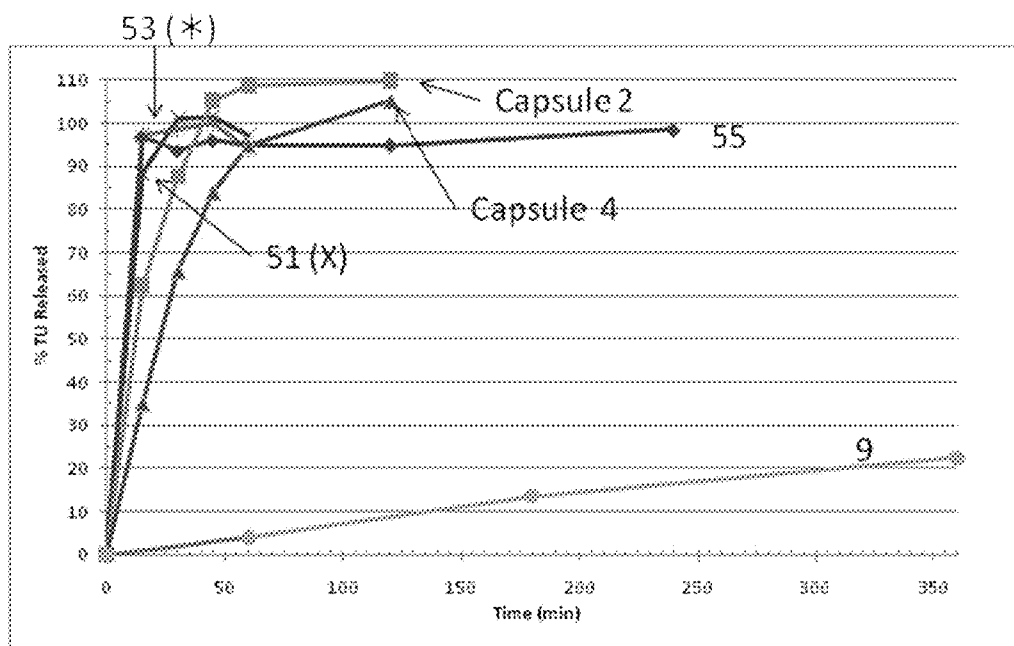
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(57) **ABSTRACT**

Methods for modulating one or more side effects of 5- α -reductase inhibitor therapy are provided, where the method includes administering a 5- α -reductase inhibitor and testosterone undecanoate. Also provided are methods of maintaining or restoring a DHT serum level in an individual undergoing 5- α -reductase inhibitor therapy, where the method includes administering testosterone undecanoate in addition to 5- α -reductase inhibitor. Further provided are methods of treating or preventing a DHT-related condition, such as benign prostate hyperplasia (BPH) or prostate cancer by administering a 5- α -reductase inhibitor and testosterone undecanoate.

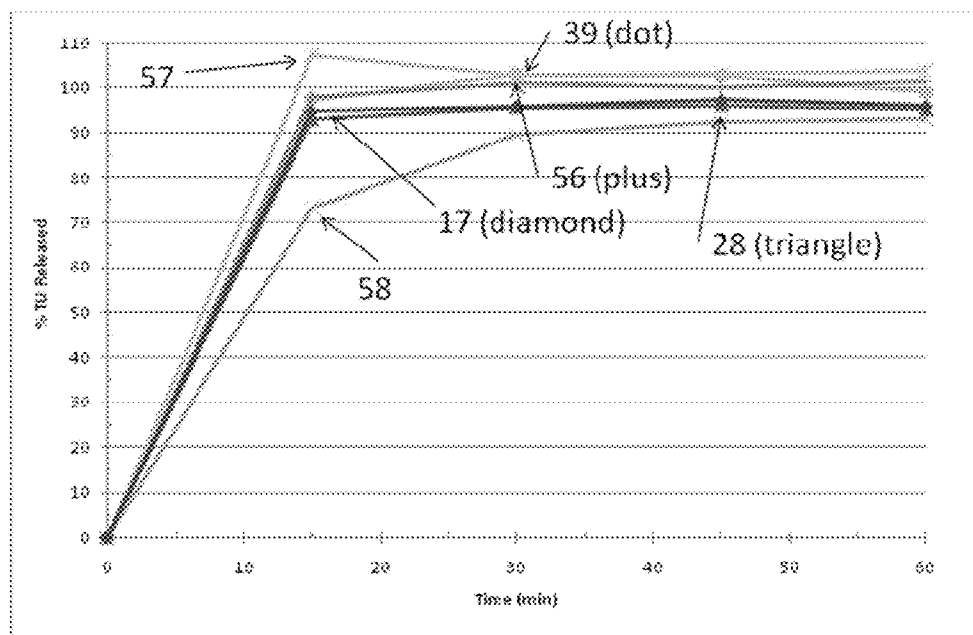
**FIG. 1**



Dissolution (USP 2 apparatus) of testosterone undecanoate formulations

- ▲: Formulation described by Capsule 4 of Example 1 US2010/0173882
- : Formulation described by Capsule 2 of Example 1 of US2010/0173882
- ◆: Formulation 55 of Table 20
- X: Formulation 51 of Table 20
- *: Formulation 53 of Table 20
- : Formulation 9 of Table 2

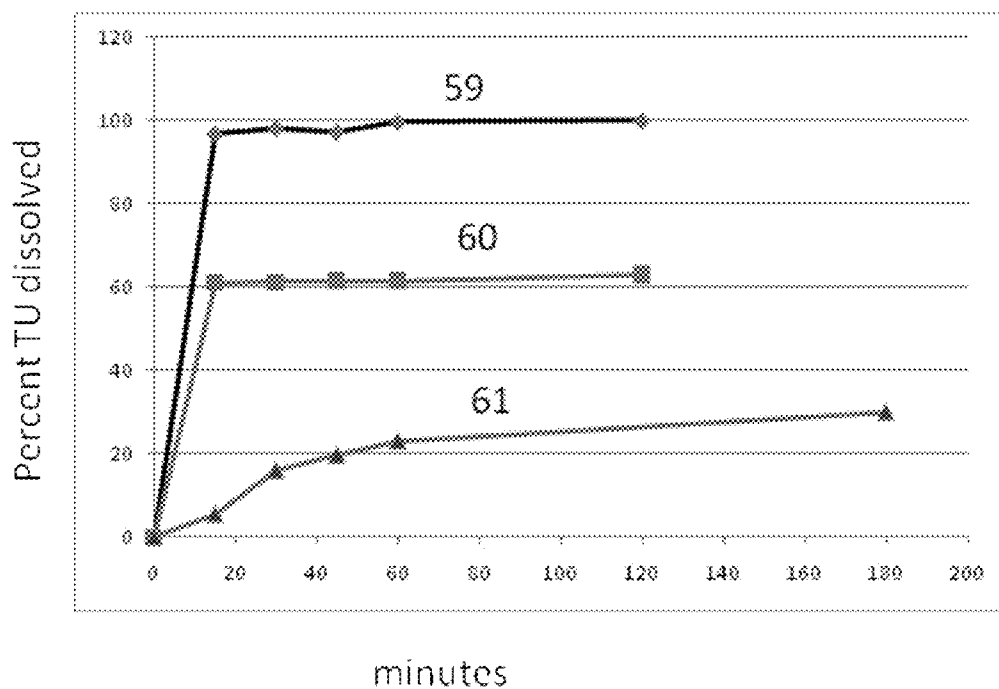
FIG. 2



Dissolution (USP 2 apparatus) of testosterone undecanoate formulations (80mg TU)

- ▲: Formulation 28 of Table 10
- : Formulation 39 of Table 14
- +: Formulation 56 of Table 27
- *: Formulation 57 of Table 27
- X: Formulation 58 of Table 21
- ◆: Formulation 17 of Table 5

FIG. 3



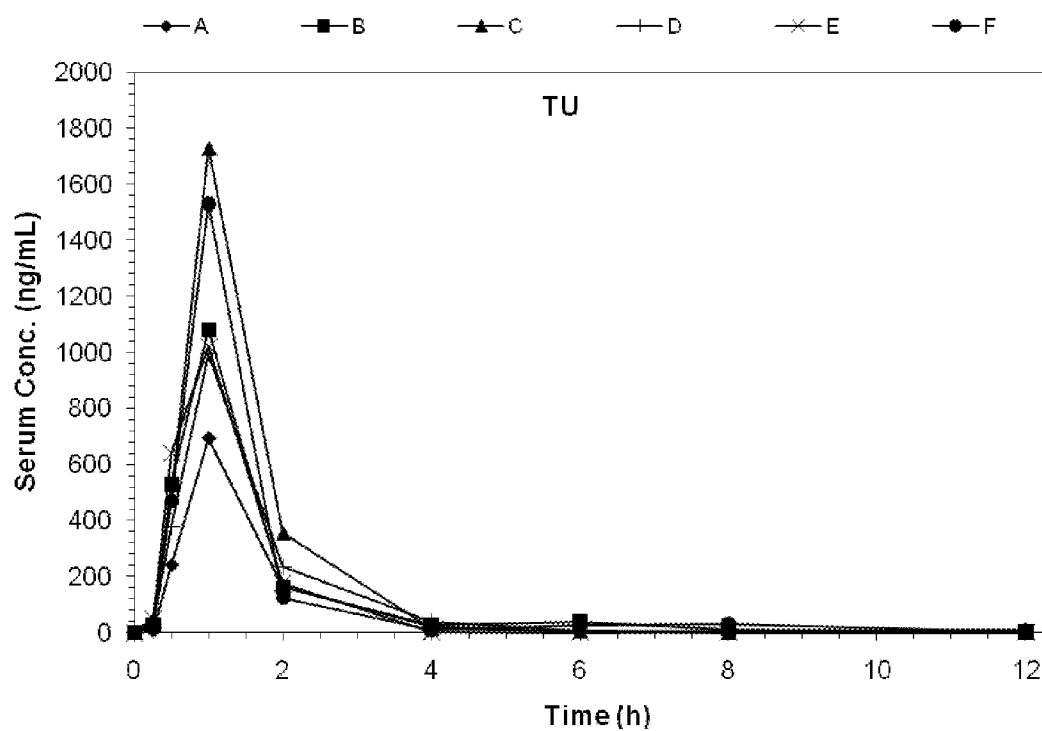
Dissolution (USP 2 apparatus) of testosterone undecanoate formulations

◆: Formulation 59 of Table 22

■: Formulation 60 of Table 22

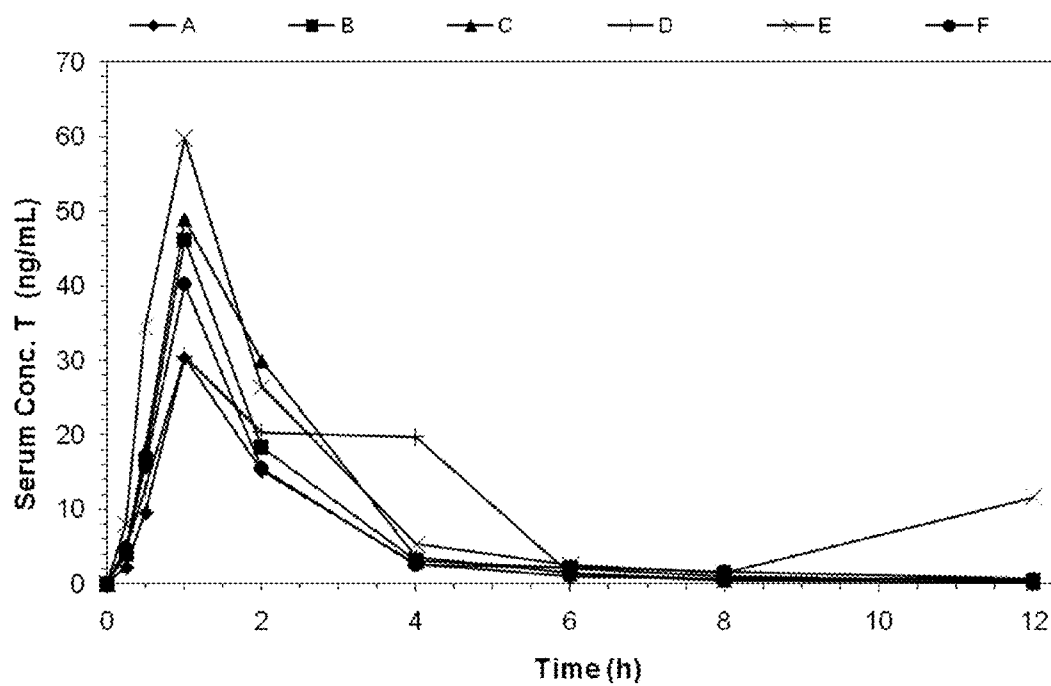
▲: Formulation 61 of Table 22

FIG. 4



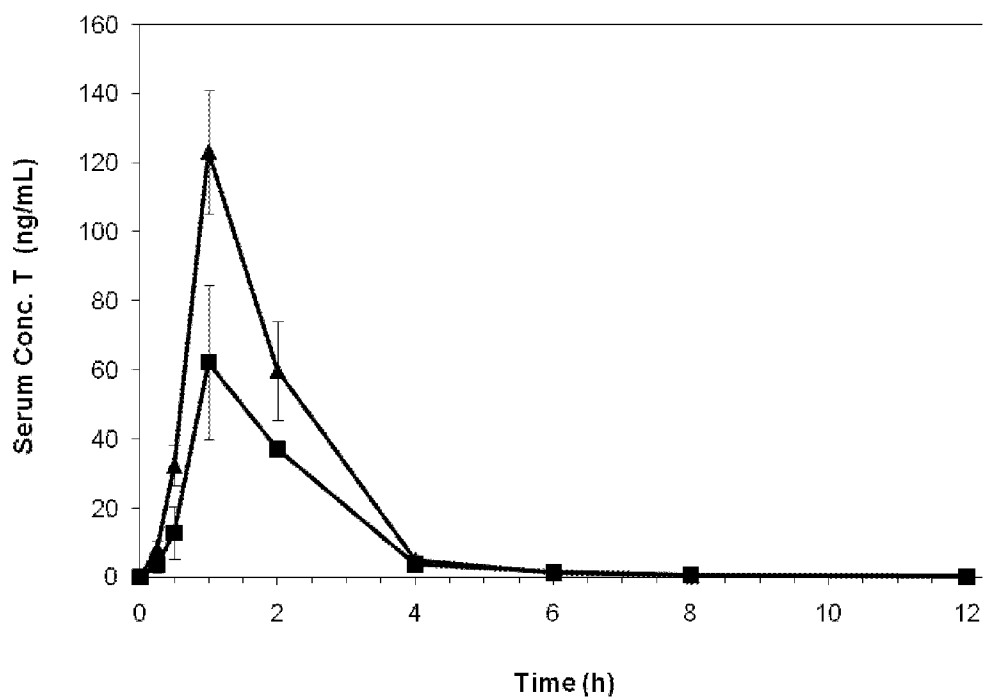
Mean testosterone undecanoate pharmacokinetic profiles in beagle dogs of treatments A-F of Table 23, Example 4.

FIG. 5A



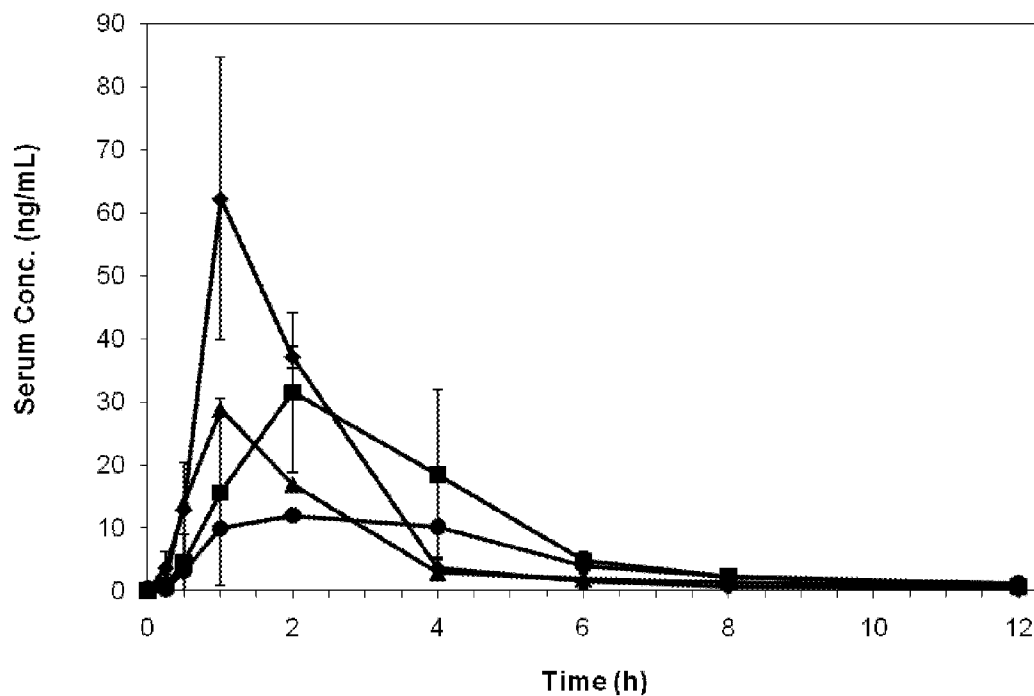
Mean testosterone pharmacokinetic profiles in beagle dogs of treatments A-F of Table 23, Example 4.

FIG. 5B



Mean testosterone pharmacokinetic profile in beagle dogs of Formulation 54 (▲) and Formulation 52 (■) of Table 20 and Example 5.

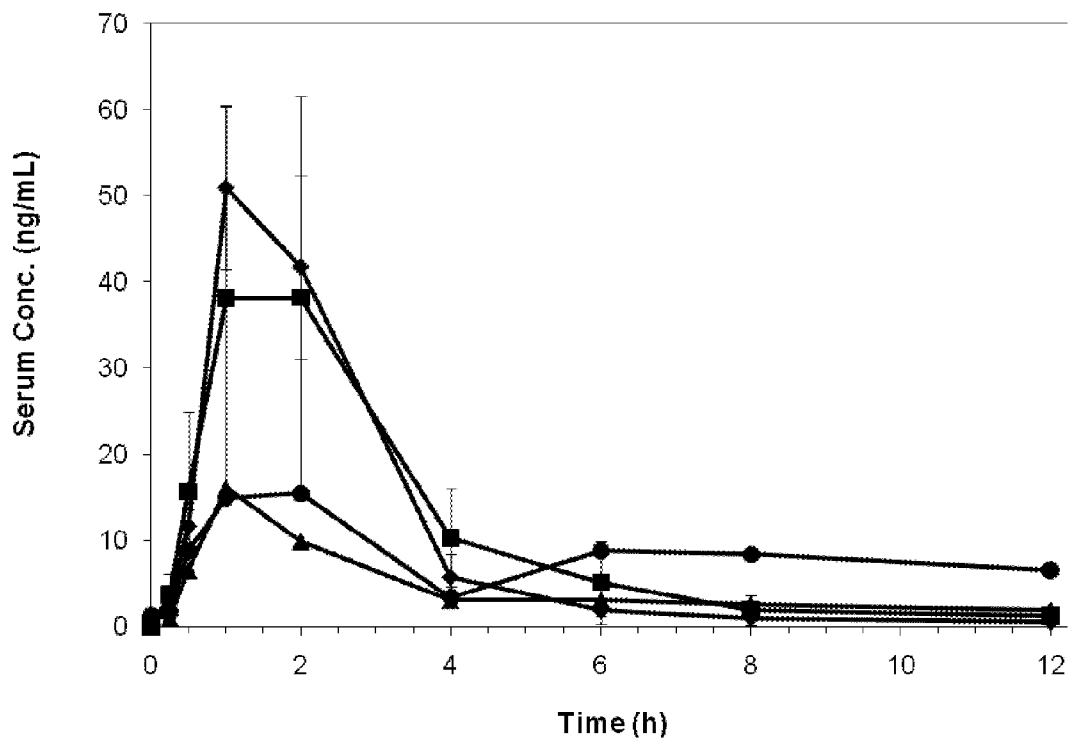
FIG. 6



Mean testosterone and dihydrotestosterone pharmacokinetic profile in beagle dogs of Formulation 52 with and without finasteride.

- ◆ Testosterone concentrations, Formulation 52 (80mg TU) dosed without finasteride
- ▲ Testosterone concentrations, Formulation 52 (80mg TU) dosed with finasteride
- Dihydrotestosterone concentrations, Formulation 52 (80mg TU) dosed without finasteride
- Dihydrotestosterone concentrations, Formulation 52 (80mg TU) dosed without finasteride

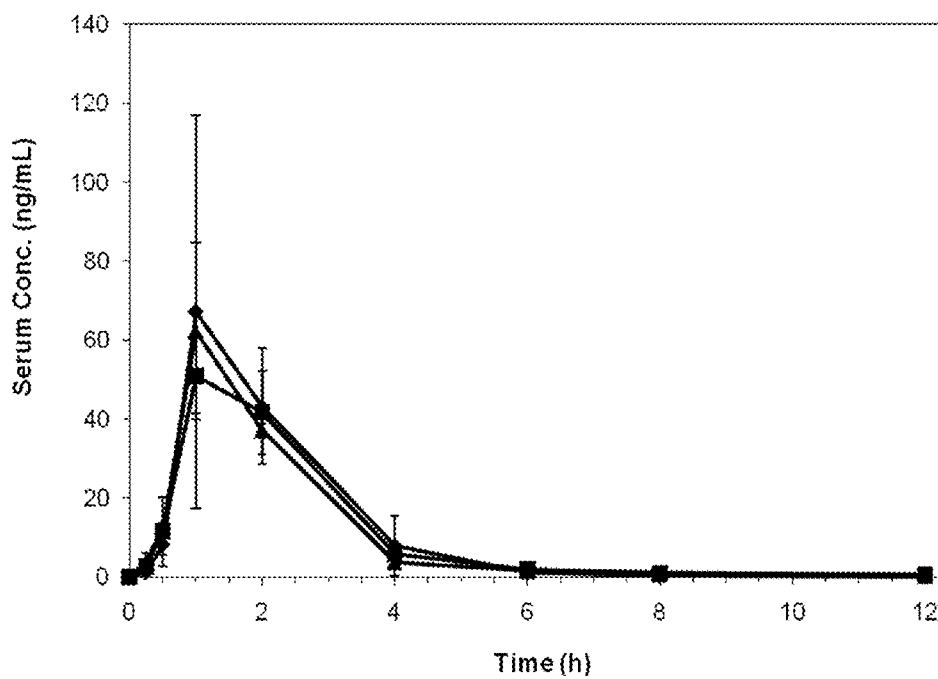
FIG. 7



Mean testosterone and dihydrotestosterone pharmacokinetic profile in beagle dogs of Formulation 52 with and without dutasteride.

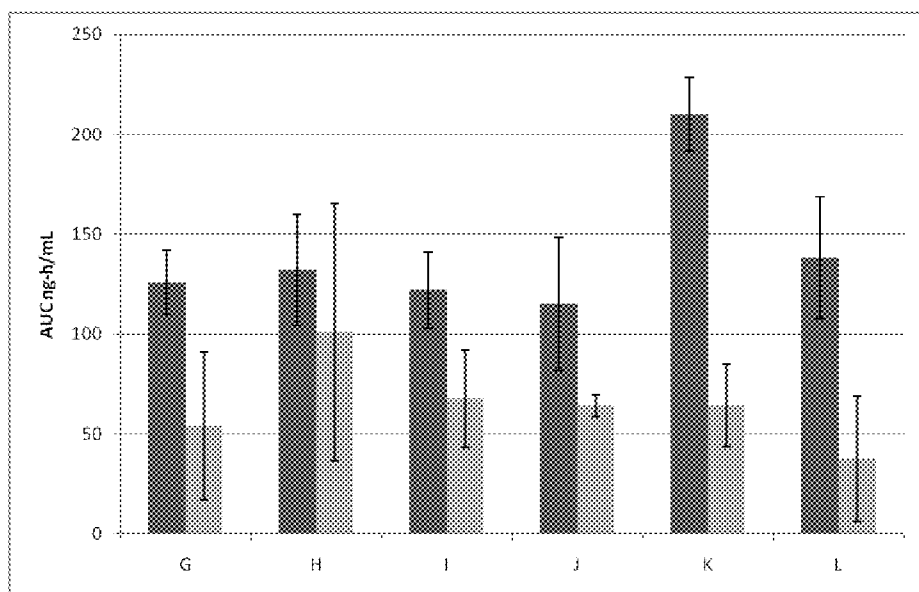
- ◆ Testosterone concentrations, Formulation 52 (80mg TU) dosed without dutasteride
- Testosterone concentrations, Formulation 52 (80mg TU) dosed with dutasteride
- ▲ Dihydrotestosterone concentrations, Formulation 52 (80mg TU) dosed without dutasteride
- Dihydrotestosterone concentrations, Formulation 52 (80mg TU) dosed without dutasteride

FIG. 8



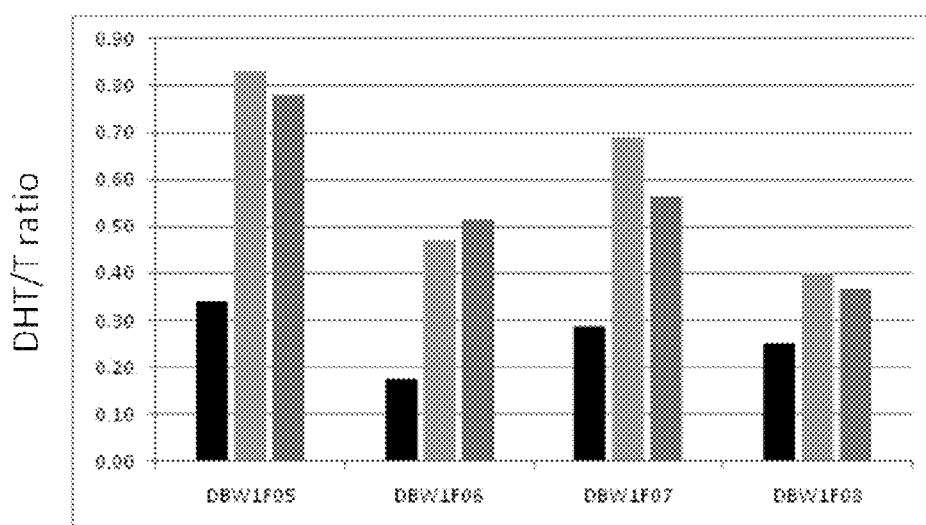
Mean testosterone pharmacokinetic profile in beagle dogs of Formulation 52 with 400mg (▲ and ■) and 800mg (◆) of phytosterols.

FIG. 9



Mean testosterone (dark bar) and dihydrotestosterone (light bar) exposures resulting from Treatments G through L, Table 24, Example 5. Error bars represent plus and minus one standard deviation.

FIG. 10



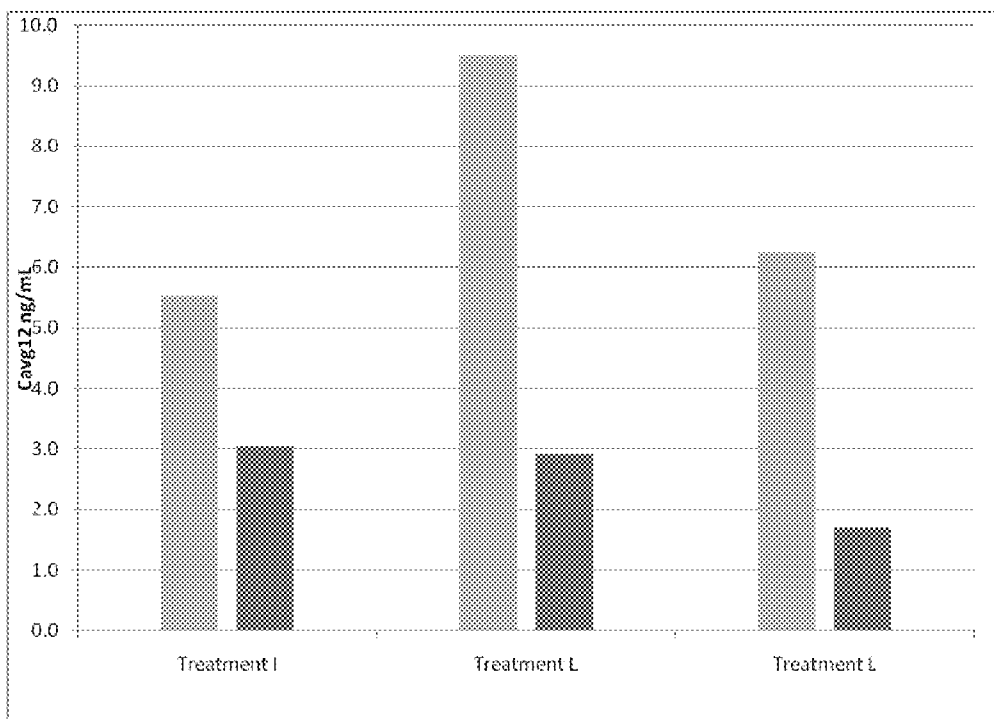
Ratio of dihydrotestosterone to testosterone in four beagle dogs dosed with treatments as described in Example 5.

First bar: Treatment K, Table 24

Second bar: Treatment I, Table 24

Third bar: Treatment J, Table 24

FIG. 11



Predicted human values of testosterone (first bar) and dihydrotestosterone (second bar) based on Treatments I, L, and K from Example 5, for 80mg testosterone undecanoate single dose

FIG. 12

MODULATION OF SIDE EFFECT PROFILE OF 5-ALPHA REDUCTASE INHIBITOR THERAPY

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This is a continuation in part of U.S. patent application Ser. No. 12/983,216, filed Dec. 31, 2010, which claims the benefit of U.S. Provisional Patent Application No. 61/291,769, filed Dec. 31, 2009. The disclosures of the foregoing applications are hereby incorporated herein by reference in their respective entireties, for all purposes.

FIELD OF THE INVENTION

[0002] The present invention relates to methods for modulating the side effect profile of 5- α -reductase inhibitor therapy treatment of DHT-related conditions by administration of testosterone undecanoate in addition to a 5- α -reductase inhibitor. The invention further relates to methods of maintaining or restoring a serum DHT level in an individual undergoing 5- α -reductase inhibitor therapy.

DESCRIPTION OF THE RELATED ART

[0003] Testosterone is one of the most important androgens synthesized in the body. It is formed mainly in the testicles and in small amounts in the adrenal glands and in women in the ovaries. In males, testosterone is responsible for the development of the male characteristics during fetal, neonatal and pubertal maturation and finally for attaining the male phenotype and for androgen-dependent functions (for example spermatogenesis). Testosterone exerts protein-anabolic action (in muscles, bones, hematopoiesis, kidneys and liver) (E. Mutschler, "Arzneimittelwirkungen" [Drug Actions], 6th edition, pp. 334-337, Wissenschaftliche Verlagsgesellschaft mbh [publisher], Stuttgart, 1991.).

[0004] The use of testosterone and other androgens as a replacement therapy to restore or increase testosterone levels or provide other effects associated with androgens for a variety of medical conditions is well-established. (Corona, G., *J Sex Med*, 639-654(2011); Bhasin, S., *Nat Clin Pract Endocrinol metab.*, 146-159 (2006)) A variety of dosage forms are used, including topical sprays or gels containing testosterone, injections of testosterone or testosterone esters in oily vehicles, implantation of pellets containing testosterone, buccal formulations of testosterone, oral formulations of testosterone esters and dermal patches containing testosterone. In the case of oral formulations of testosterone undecanoate, the ester acts as a pro-drug for testosterone. Testosterone is released by cleavage of the ester linkage by physiological esterases. Testosterone undecanoate has the advantage of being absorbed by the lymphatic system, avoiding the first pass hepatic metabolism that severely limits the utility of oral dosing of testosterone (Shackleford, D. (2003). *J Pharmacology Experimental Therapeutics*, 925-933.)

[0005] Testosterone products currently on the market utilize oral, parenteral, intramuscular, transdermal, sublingual, and/or buccal routes of administration. Oral, and transdermal administration is particularly challenging because in humans and other mammals testosterone is metabolized by 5- α -reductase enzyme to dihydrotestosterone (DHT) resulting in supraphysiological levels of DHT. DHT is a more potent androgen than testosterone.

[0006] The 5- α -reductase enzyme is known to exist in at least two forms, commonly known as Type I and Type II. Type I 5- α -reductase is the dominant form expressed in the skin and liver, while Type II is the dominant type expressed in the prostate but is also found in the liver. (McConnell, John D., (2001). *Advances in Protein Chemistry*, Volume 56, 2001, Pages 143-180. American Chemical Society.)

[0007] Two 5- α -reductase inhibitors, finasteride and dutasteride, are commonly used for treatment of conditions related to the presence of DHT. Finasteride is primarily an inhibitor of Type II 5- α -reductase (David W. Russell, *Annual Review Biochemistry*, 25-61 (1994).) Dutasteride is an inhibitor of both Type I and Type II forms of the 5- α -reductase reductase enzyme (Abdulmageed M. Traish, *J Sex Med*, 872-884 (2011)). Commercial preparations of finasteride and dutasteride are known, e.g. Proscar®, Propecia®, and Avodart®. Both finasteride and dutasteride are used in the treatment of benign prostate hyperplasia (BPH). Finasteride is also used in the treatment of alopecia (hair loss). Additionally, both dutasteride and finasteride have been studied in connection with the prevention of prostate cancer (Abdulmageed M. Traish, (2011)).

[0008] The oral administration of 5- α -reductase inhibitors leads to systemic inhibition of the reduction of testosterone to DHT. Since DHT is a significant androgen in human physiology, the systemic inhibition of the 5- α -reductase enzyme and the resultant sub-physiological levels of DHT may lead to effects unrelated to the goal of treating a localized condition or disease (e.g. BPH or alopecia). Undesired systemic side effects of the use of 5- α -reductase inhibitors include effects on libido, erectile function, ejaculatory function, breast tissue, depression, acne, muscle weakness, prostatic hyperplasia and male pattern baldness, among others.

[0009] Amory and Bremner studied the pharmacokinetics of oral testosterone or testosterone enanthate in a lipid formulation co-dosed with the 5- α -reductase inhibitor dutasteride. (Amory, J. K., *J Clin Endocrinol Metab*, 2610-2617 (2005).) The co-dosing of testosterone with dutasteride resulted in increased levels of serum testosterone compared to dosing with testosterone alone. Additionally, serum DHT levels were suppressed by the co-administration of dutasteride with testosterone or testosterone enanthate compared to the serum DHT levels observed with administration of testosterone or testosterone enanthate alone.

[0010] Roth et al. studied the pharmacokinetics of the addition of the 5- α -reductase inhibitor finasteride to an oral testosterone undecanoate (TU) therapy, in order to prevent elevated DHT. (M. Y. Roth, *Intl J. of Andrology*, 1-7 (2010)). Roth et al. hypothesized that addition of finasteride to the TU therapy would increase serum testosterone and lower DHT, similar to the effects seen with testosterone. Instead, surprisingly, they observed that by administration of TU, serum DHT levels were significantly elevated and that co-administration of finasteride with TU had no significant effect on either of serum testosterone levels or serum DHT levels. Roth et al. theorized that the difference of TU, as compared to other testosterone formulations may be due to the lymphatic route of absorption.

[0011] Borst et al. demonstrated that administration of a 5- α -reductase inhibitor, MK-434, to rats in combination with testosterone produced systemic anabolic effects with little effect on prostate size. (Borst, S. E., *Am J Physiol Endocrinol Metab*, E222-E227 (2005).) The intra-prostatic DHT levels were increased over the intra-prostatic DHT levels observed

without exogenous testosterone, but were markedly reduced from levels observed in the absence of MK-434. Serum levels of DHT were approximately the same whether testosterone was co-administered with MK-434 or alone.

[0012] The persistence of DHT in the prostate at levels of 20-30% has been demonstrated in male subjects whose serum testosterone levels were medically decreased by greater than 90%. Further, Page and co-workers demonstrated that transdermal dosing of dihydrotestosterone did not result in an increase in DHT levels within the prostate. Similarly, Nishiyama and co-workers showed that DHT remained present in the prostate at approximately 25% of the level observed before androgen deprivation therapy. (Page, S. T., *J Endocrinol Metab*, 430-437 (2011) (Page, S. T., *J Endocrinol Metab*, 3850-3856 (2006); Mostaghel, E. A., *Cancer Research*, 5033-5041, (2007); Nishiyama, T., *Clinical Cancer Research*, 7121-7126, (2004).) Taken together, these studies show that there is not necessarily a correlation between intra-prostatic DHT levels and systemic DHT levels.

[0013] Accordingly, it is desirable to develop alternative therapies that modulate the side effect profile of 5- α reductase inhibitor therapy.

SUMMARY OF THE INVENTION

[0014] The present invention relates to methods of modulating the effects of 5- α -reductase inhibitor therapy.

[0015] In one aspect the invention provides a method of modulating one or more side effects of 5- α -reductase inhibitor therapy, the method comprising administering: a 5- α -reductase inhibitor and testosterone undecanoate, wherein the administration of testosterone undecanoate is effective to modulate one or more side effects of the 5- α -reductase inhibitor administration.

[0016] In another aspect the invention provides a method of maintaining or restoring a serum DHT level in an individual undergoing 5- α -reductase inhibitor therapy, the method comprising administration of testosterone undecanoate in addition to a 5- α -reductase inhibitor.

[0017] In a further aspect the invention provides a method of treating or preventing a DHT-related condition, the method comprising administering: a 5- α -reductase inhibitor and testosterone undecanoate.

[0018] Other aspects, features and embodiments of the invention will be more fully apparent from the ensuing disclosure and appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] FIG. 1 is a flowchart of the process used to obtain formulations of the invention (Table 20), as described in Example 8.

[0020] FIG. 2 shows dissolution curves of testosterone undecanoate Formulations 9 (Table 2), 51, 53 and 55 (Table 20), as compared to known preparations described in Example 1 of US2010/0173882.

[0021] FIG. 3 shows dissolution curves of testosterone undecanoate Formulations 17 (Table 5), 28 (Table 10), 39 (Table 14), 56, 57 (Table 27) and 58 (Table 21).

[0022] FIG. 4 shows dissolution curves of testosterone undecanoate from formulations 59, 60, and 61 (Table 22).

[0023] FIG. 5A is a mean PK profile of testosterone undecanoate resulting from treatments A through F described in

Table 23 dosed to 4 beagle dogs after eating a high fat meal. FIG. 5B is the mean PK profile of testosterone for the same treatments A-F.

[0024] FIG. 6 shows the mean testosterone concentration in beagle dogs dosed with 80 mg testosterone undecanoate in Formulations 54 and 52 (Table 20). Values are the mean values obtained from a single group of 4 dogs. Phytosterols (400 mg) were co-dosed on both occasions

[0025] FIG. 7 shows the mean testosterone and DHT concentration profile in 4 beagle dogs dosed with 80 mg testosterone undecanoate in formulation 52 (Table 20), with and without 5 mg finasteride. Phytosterols (400 mg) were co-dosed on both occasions.

[0026] FIG. 8 shows the mean testosterone and DHT concentration profile in 4 beagle dogs dosed with 80 mg testosterone undecanoate in formulation 52 (Table 20), with and without 0.5 mg dutasteride. Phytosterols (400 mg) were co-dosed on both occasions.

[0027] FIG. 9 shows the mean testosterone concentration profile in three beagle dog groups (4 per group) dosed with 80 mg testosterone undecanoate in formulation 52 (Table 20) and 400 or 800 mg of phytosterols.

[0028] FIG. 10 shows the average testosterone and DHT exposures (ng-h/mL) for a study of 6 treatments G-L each containing 80 mg TU, as provided in Example 5.

[0029] FIG. 11 shows the DHT/T ratios for 4 beagle dogs dosed with three treatments each containing 80 mg TU, as provided in Example 5. All treatments were co-dosed with 400 mg phytosterols.

[0030] FIG. 12 shows the predicted average human concentrations of testosterone and DHT resulting from dosing with Treatments I, K, and L as described in Table 24.

DETAILED DESCRIPTION OF THE INVENTION, AND PREFERRED EMBODIMENTS THEREOF

[0031] The present invention relates to improved formulations and methods (e.g., oral, parenteral, intramuscular, transdermal, nasal, sublingual, buccal and/or subcutaneous) for drug delivery involving modulation of solubility, stability, absorption, metabolism, and/or pharmacokinetic profile of the therapeutic agent when administered to a subject in need of such therapeutic agent.

[0032] Prior androgen replacement therapies including administration of an inhibitor of 5- α -reductase enzymes to control DHT production resulted in systemic deficiency of DHT and undesired side effects. Additionally, therapies for BPH and other DHT-related conditions including administration of an inhibitor of 5- α -reductase enzymes similarly result in systemic deficiency of DHT and undesired side effects. The present invention relates to the use of testosterone esters, particularly testosterone undecanoate, to maintain systemic levels of DHT in an individual undergoing 5- α -reductase enzyme inhibitor therapy.

[0033] It is noted that as used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise.

[0034] Specifically, a formulation or composition of the invention includes a combination of one or more therapeutic agents and a sterol or sterol ester, where inclusion of the sterol or sterol ester provides an additive or synergistic effect with respect to one or more of: solubility, stability, absorption, metabolism, and pharmacokinetic profile of the therapeutic agent. By inclusion of a sterol or sterol ester, smaller amounts of a therapeutic agent are required in the formulation, to

achieve a desired pharmacokinetic profile of the therapeutic agent in the subject that is similar to that achieved with a larger amount of therapeutic agent administered without the sterol or sterol ester. In a preferred embodiment the sterol is a phytosterol. A formulation of the invention further includes a non-sterol solubilizer to further modulate the pharmacokinetic profile of the therapeutic agent upon administration of the formulation.

[0035] The formulations described herein contain a therapeutic agent in a substantially solubilized form. The formulations improve the bioavailability and pharmacokinetic profile of the therapeutic agent after oral, parenteral, intramuscular, transdermal, nasal, sublingual, buccal and/or subcutaneous administration and/or improve patient compliance through an easily followed dosing regimen.

[0036] The invention further provides pharmaceutical compositions containing such formulations and methods of making and methods of using such formulations.

[0037] The formulations of the invention are formulations for the oral, parenteral, intramuscular, transdermal, nasal, sublingual, buccal and/or subcutaneous administration of a therapeutic agent. The therapeutic agent contained in such formulation can be generally lipophilic in nature (with a log P greater than 2, wherein P is the intrinsic octanol:water partition coefficient) and poorly water soluble. "Poorly water soluble," as referred to herein, refers to drugs for which the dose is not soluble in 250 mL of aqueous solution across a pH range of 1.0 to 7.5. This definition is used in The Biopharmaceutics Classification System (BCS) Guidance published in 2005 by the US Food and Drug Administration. "Lipophilic" as used herein refers to a therapeutic agent that is soluble in lipids, such as fats, oils, and the like. Accordingly, in one embodiment, the invention provides a formulation where a lipid is provided as a solubilizer with the therapeutic agent, so that the administered therapeutic agent is bioavailable, exhibits desirable pharmacokinetic profile and any effects of food on the oral bioavailability of the therapeutic agent are minimized. Furthermore, hydrophobic drugs defined herein encompass both those drugs which are inherently hydrophobic (i.e., having a log P of at least 2) as well otherwise hydrophobic medicaments that have been rendered hydrophobic with suitable modification (e.g., by conjugation to fatty acids and/or lipids).

[0038] The therapeutic agent herein may also be referred to herein as an "active agent," "drug" or "pharmacologically active agent." The above-listed terms interchangeably refer to a chemical material or compound which, when administered to an organism (human or animal), is generally bioavailable and induces a desired pharmacologic effect.

[0039] Examples of therapeutic agents having the above-described characteristics and therefore capable of administration in formulations of the invention include, but are not limited to: analgesics, anti-inflammatory agents, anti-helminthics, anti-arrhythmic agents, anti-asthma agents, anti-bacterial agents, anti-viral agents, anti-coagulants, anti-depressants, anti-diabetics, anti-epileptics, anti-fungal agents, anti-gout agents, anti-hypertensive agents, anti-malarials, anti-migraine agents, anti-muscarinic agents, anti-neoplastic agents, immunosuppressants, anti-protozoal agents, anti-thyroid agents, anti-tussives, anxiolytics, sedatives, hypnotics, neuroleptics, β -blockers, cardiac inotropic agents, cell adhesion inhibitors, corticosteroids, cytokine receptor activity modulators, diuretics, anti-parkinsonian agents, gastro-intestinal agents, histamine H₂-receptor antagonists, keratolytics,

lipid regulating agents, muscle relaxants, nitrates and other anti-anginal agents, non-steroid anti-asthma agents, nutritional agents, opioid analgesics, sex hormones, stimulants and anti-erectile dysfunction agents.

[0040] Additionally, the therapeutic agent may be selected from any agent that is traditionally used as a medicament and lends itself to being administered via oral or parenteral (such as intramuscular, transdermal, nasal, sublingual, buccal and subcutaneous) routes of administration. Such therapeutic agents may be chemotherapeutics; antimycotics; oral contraceptives, nicotine or nicotine replacement agents, minerals, analgesics, antacids, muscle relaxants, antihistamines, decongestants, anesthetics, antitussives, diuretics, anti-inflammatories, antibiotics, antivirals, psychotherapeutic agents, anti-diabetic agents and cardiovascular agents, nutraceuticals and nutritional supplements.

[0041] Additional therapeutic agents for administration via formulations of the invention include vitamins and co-enzymes including, but not limited to, water or fat soluble vitamins such as thiamin, riboflavin, nicotinic acid, pyridoxine, pantothenic acid, biotin, flavin, choline, inositol and paminobenzoic acid, carnitine, vitamin C, vitamin D and its analogs, vitamin A and the carotenoids, retinoic acid, vitamin E and vitamin K and Coenzyme Q10.

[0042] The therapeutic agent of formulations of the invention may also be selected from botanical bioactive agents, such as: polyphenols, isoflavones, resveratrol, soy isoflavones, grape seed extract polyphenols, curcumin, policosanols, and epigenin; anti-inflammatory plant extracts such as aloe vera, echinacea and chamomile hammamelis extracts; anti-psoriatic plant extracts, such as chinese zizipus jujube; astringents plant extracts such as hammamelis; anti bacterial plant extracts such as artemisia, chamomile, and golden seal; immune modulators such as Echinacea; anti-aging or anti-cancer or anti-photo damage agents; anti-inflammatory agents, such as feverfew parthenolides, rejuvenation agents, carotenoids, beta-carotene, lycopene, astaxanthons, lutein, tocopheryl and retinol.

[0043] The therapeutic agent of formulations of the invention may also include coronary drugs, including vasodilators such as nitroglycerin and isosorbide dinitrate, calcium-antagonists such as verapamil, nifedipine and diltiazem, and cardiac-glycosides such as digoxine. Other therapeutic agents that can be usefully administered in the broad practice of the invention include analgesics such as morphine, buprenorphine, etc., and local anesthetics such as lidocaine, and the like.

[0044] Still further, the therapeutic agent of a formulation of the invention may be selected from cholesterol-lowering and triglycerides-lowering drugs: fenofibrate, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, or cerivastatin; anxiolytics, sedatives and hypnotics: diazepam, nitrazepam, flurazepam, estazolam, flunitrazepam, triazolam, alprazolam, midazolam, temazepam, lorazepam, lorazepam, brotizolam, clobazam, clonazepam, lorazepam, oxazepam, buspirone, and the like; migraine relieving agents: sumatriptan, ergotamines and derivatives, and the like; drugs for combating motion sickness: cinnarizine, anti-histamines, and the like; anti-emetics: ondansetron, tropisetron, granisetron, metoclopramide, and the like; disulfiram; and vitamin K.

[0045] Further examples of therapeutic agents for use in formulations of the invention include: chemotherapeutic agents, including, but not limited to: cisplatin (CDDP), procarbazine, mechlorethamine, cyclophosphamide, camptoth-

ecin, ifosfamide, melphalan, chlorambucil, bisulfan, nitrosurea, dactinomycin, daunorubicin, doxorubicin, bleomycin, plicomycin, mitomycin, etoposide (VP16), tamoxifen, taxol, transplatinum, 5-fluorouracil, vincristin, vinblastin and methotrexate, or any analog or derivative variant thereof; antibiotic drugs: Tetracyclines such as tetracycline, doxycycline, oxytetracycline, chloramphenicol etc.; Macrolides such as erythromycin and derivatives, etc.; Antivirals: such as acyclovir, idoxuridine, tromantadine etc.; Antimycotics: Miconazole, ketoconazole, fluconazole, itraconazole, econazole, terconazole, griseofulvin, and polyenes such as amphotericin B or nystatine etc. Anti-amoebics: Metronidazole, metronidazole benzoate and timidazole etc.; Anti-inflammatory drugs: steroids or NSAIDs such as indomethacin, ibuprofen, piroxicam, diclofenac etc.; Anti-allergics: Disodium cromoglycate etc.; Immunosuppressive agents: cyclosporine etc.; Antimicrobial agents that may be used include, but are not limited to, nafcillin, oxacillin, vancomycin, clindamycin, erythromycin, trimethoprim-sulphamethoxazole, rifampin, ciprofloxacin, broad spectrum penicillin, amoxicillin, gentamicin, ceftriaxone, cefotaxime, chloramphenicol, clavulanate, sulbactam, probenecid, doxycycline, spectinomycin, cefixime, penicillin G, minocycline, β -lactamase inhibitors; meziocillin, piperacillin, aztreonam, norfloxacin, trimethoprim, ceftazidime, ceftriaxone and dapsone; Antifungal agents include, but are not limited to: ketoconazole, fluconazole, nystatin, itraconazole, clotrimazole, and amphotericin B. Antiviral agents, include, but are not limited to: acyclovir, trifluridine, idoxorudine, foscarnet, ganciclovir, zidovudine, dideoxycytosine, dideoxyinosine, stavudine, fampiclovir, didanosine, zalcitabine, rifimantadine, and cytokines. Anti-histamines useful for therapeutic administration include, but are not limited to: cimetidine, ranitidine, diphenhydramine, prylamine, promethazine, chlorpheniramine, chlorcyclizine, terfenadine, carbinoxamine maleate, clemastine fumarate, diphenhydramine hydrochloride, dimenhydrinate, prilamine maleate, tripeleannamine hydrochloride, tripeleannamine citrate, chlorpheniramine maleate, brompheniramine maleate, hydroxyzine pamoate, hydroxyzine hydrochloride, cyclizine lactate, cyclizine hydrochloride, meclizine hydrochloride, acrivastine, cetirizine hydrochloride, astemizole, levocabastine hydrochloride, and loratadine. Decongestants and antitussives include, but are not limited to: dextromethorphan, levopropoxyphene napsylate, noscapine, carbetapentane, caramiphen, chlophedianol, pseudoephedrine hydrochloride, diphenhydramine, glaucine, pholcodine, and benzonatate. Other therapeutic agents administrable in formulations of the invention include: anesthetics, such as: etomidate, ketamine, propofol, and benodiazapines (e.g., chlordiazepoxide, diazepam, clonazepam, halazepam, flurazepam, quazepam, estazolam, triazolam, alprozolam, midazolam, temazepam, oxazepam, lorazepam), benzocaine, dyclonine, bupivacaine, etidocaine, lidocaine, mepivacaine, promoxine, prilocalne, procaine, proparacaine, ropivacaine, and tetracaine. Other useful agents may include: amobarbital, aprobarbital, butabarbital, butalbital mephobarbital, methohexital, pentobarbital, phenobarbital, secobarbital, thiopental, paral, chloral hydrate, ethchlorvynol, clutethimide, methprylon, ethinamate, and meprobamate; Analgesics, including, but not limited to: opioids such as morphine, meperidine, dentanyl, sufentanil, alfentanil, aspirin, acetaminophen, ibuprofen, indomethacin, naproxen, atrin, isocome, midrin, axotal, firinal, phrenilin, ergot and ergot derivatives (wigraine, cafergot, ergostat, ergomar, dihydroergotamine), imitrex; Diuretics

including, but not limited to: acetazolamide, dichlorophenamide, methazolamide, furosemide, bumetanide, ethacrynic acid torseimide, azosemide, muzolimine, piretanide, tripamide, bendroflumethiazide, benzthiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, trichlormethiazide, indapamide, metolazone, quinethazone, amiloride, triamterene, spironolactone, canrenone, and potassium canrenoate; Anti-inflammatories including, but not limited to: salicylic acid derivatives (e.g. aspirin) paraminophenol derivative (e.g. acetaminophen) indole and indene acetic acids (indomethacin, sulindac and etodalac) heteroaryl acetic acids (tolmetin diclofenac and ketorolac) aryl propionic acid derivatives (ibuprofen, naproxen, ketoprofen, fenopren, oxaprozine), anthranilic acids (mefenamic acid, meclofenamic acid) enolic acids (piroxicam, tenoxicam, phenylbutazone and oxyphenbutazone); Psychotherapeutic agents including, but not limited to: thiazine, serentil, mellaril, miltazine, tindal, permitil, prolixin, trilafon, stelazine, suprazine, taractan, navan, clozaril, haldol, halperon, loxitane, moban, orap, risperdal, alprazolam, chlordiazepoxide, clonazepam, clonazepam, diazepam, halazepam, lorazepam, oxazepam, prazepam, buspirone, elvavil, anafanil, adapin, sinequan, tofranil, surmontil, asendin, norpramin, pertofrane, ludiomil, pamelor, vivactil, prozac, luvox, paxil, zoloft, effexor, serzone, desyrel, nardil, parnate, eldepryl; Cardiovascular agents including, but not limited to: nitroglycerin, isosorbide dinitrate, sodium nitroprusside, captopril, enalapril, enalaprilat, quinapril, lisinopril, ramipril, losartan, aminone, lirinone, vesnerinone, hydralazine, nicorandil, prozasin, doxazosin, bunazosin, tamulosin, yohimbine, propranolol, metoprolol, nadolol, atenolol, timolol, esmolol, pindolol, acebutolol, labetalol, phentolamine, carvedilol, bucindolol, verapamil, nifedipine, amlodipine and dobutamine.

[0046] The compositions of the invention, in various embodiments provide effective formulations for oral, parenteral, intramuscular, transdermal, nasal, sublingual, buccal and/or subcutaneous administration of androgens as the therapeutic agent.

[0047] Androgens have diverse effects in many tissues. Recent studies have begun to elucidate the mechanisms of their anabolic effects. The mechanistic understanding is leading to an increase in clinical usefulness for many disease states. The strongest indication for the use of androgens is for replacement therapy in hypogonadal men to maintain sexual function and libido, muscle strength, and prevent the development of osteoporosis. Another use is for the stimulation of erythropoiesis in condition of bone marrow suppression such as aplastic anaemia.

[0048] As men age, testosterone concentrations are reduced and considerable interest has developed over the use of physiologic doses of testosterone to return concentrations to the level of young men. Testosterone administration increases muscle protein synthesis, muscle strength, improve mood and quality of life in older men. There is also considerable interest in the use of androgens as replacement therapy in post-menopausal women and the benefits of improvement in muscle strength, sexuality and libido are compelling in this group of women.

[0049] Androgens have also shown clinical usefulness in the treatment of muscle wasting syndromes. In men with AIDS wasting syndrome, there was a direct relationship between the loss of lean body mass and the degree of hypogonadism present in the disease. Testosterone replacement in

men and women with AIDS wasting syndrome increases weight gain in this debilitating condition. Androgens have also shown anabolic effects on muscular dystrophy, metabolic syndrome, and Alzheimer disease (Diab. Nutr. Metab. 12:339-343, 1999).

[0050] Androgen-containing formulations are therefore of interest in preparations for male contraception and male HRT (hormone replacement therapy). Androgens can also be used in the female, e.g. as androgen replacement therapy in postmenopausal women. Androgens may particularly be used as a replacement for or a supplement to endogenous testosterone. Thus, e.g., in male HRT, androgen is administered in order to relieve the undesired effects of the (partial) androgen-deficiency including, but not limited to, effects on bone mineral density, changes in body composition, reduction of sexual interests and erectile dysfunction. In one embodiment, the invention provides androgen-containing formulations useful for administration of androgens to a subject in need of such administration.

[0051] In one embodiment, the therapeutic agent of a formulation of the invention may be selected from testosterone and esters thereof. Testosterone esters may include, but are not limited to, any C_1 - C_{24} esters of testosterone, including testosterone propionate, testosterone enanthate, testosterone cypionate, testosterone undecanoate, testosterone cyclohexylmethylcarbonate, and testosterone triglyceride. Additional testosterone esters can include, but are not limited to, formate, acetate, butyrate, valerate, hexanoate, heptanoate, octanoate, nonanoate, and decanoate. In one embodiment, the therapeutic agent is a testosterone ester with a carbon structure that is linear or branched, and saturated, monounsaturated or polyunsaturated.

[0052] As used herein, the identification of a carbon number range, e.g., in C_1 - C_{12} alkyl, is intended to include each of the component carbon number moieties within such range, so that each intervening carbon number and any other stated or intervening carbon number value in that stated range, is encompassed, it being further understood that sub-ranges of carbon number within specified carbon number ranges may independently be included in smaller carbon number ranges, within the scope of the invention, and that ranges of carbon numbers specifically excluding a carbon number or numbers are included in the invention, and sub-ranges excluding either or both of carbon number limits of specified ranges are also included in the invention. Accordingly, C_1 - C_{12} alkyl is intended to include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl, including straight chain as well as branched groups of such types. It therefore is to be appreciated that identification of a carbon number range, e.g., C_1 - C_{12} , as broadly applicable to a substituent moiety, enables, in specific embodiments of the invention, the carbon number range to be further restricted, as a sub-group of moieties having a carbon number range within the broader specification of the substituent moiety. By way of example, the carbon number range e.g., C_1 - C_{12} alkyl, may be more restrictively specified, in particular embodiments of the invention, to encompass sub-ranges such as C_1 - C_4 alkyl, C_2 - C_8 alkyl, C_2 - C_4 alkyl, C_3 - C_5 alkyl, or any other sub-range within the broad carbon number range.

[0053] "Alkyls" as used herein include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl and isopentyl and the like. "Aryls" as used herein includes hydrocarbons derived from benzene or a benzene derivative that are unsaturated aromatic carbocyclic groups of

from 6 to 10 carbon atoms. The aryls may have a single or multiple rings. The term "aryl" as used herein also includes substituted aryls. Examples include, but are not limited to phenyl, naphthyl, xylene, phenylethane, substituted phenyl, substituted naphthyl, substituted xylene, substituted phenylethane and the like. "Cycloalkyls" as used herein include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. In all chemical formulae herein, a range of carbon numbers will be regarded as specifying a sequence of consecutive alternative carbon-containing moieties, including all moieties containing numbers of carbon atoms intermediate the endpoint values of carbon number in the specific range as well as moieties containing numbers of carbon atoms equal to an endpoint value of the specific range, e.g., C_1 - C_6 , is inclusive of C_1 , C_2 , C_3 , C_4 , C_5 and C_6 , and each of such broader ranges may be further limitingly specified with reference to carbon numbers within such ranges, as sub-ranges thereof. Thus, for example, the range C_1 - C_6 would be inclusive of and can be further limited by specification of sub-ranges such as C_1 - C_3 , C_1 - C_4 , C_2 - C_6 , C_4 - C_6 , etc. within the scope of the broader range.

[0054] In a further embodiment of the invention, the therapeutic agent is selected from testosterone and/or testosterone undecanoate (TU). In a further embodiment, the formulation contains a combination of testosterone and one or more testosterone esters as therapeutic agents, where the ratio of testosterone to testosterone ester is from about 0:100 or 100:0 to about 1:1, preferably from about 1:10 to about 1:3 or from about 10:1 to about 3:1. In various other embodiments, the ratio of testosterone to testosterone ester may be in a range having a lower value of any of 0, 0.01, 0.05, 0.1, 0.15, 0.2, 0.33, 0.5, 1.0, 2.0 and 3.0 and having an upper value of any of 90.5, 91.0, 91.25, 91.5, 91.75, 92.0, 93.0, 94.0, 95.0, 97.5, 99.0, 99.5, 99.75, 99.9, 99.95 and 100.0. In a preferred embodiment, the formulation contains testosterone and/or TU as therapeutic agents.

[0055] As used herein, references to the amounts of therapeutic agents as percent by weight of a formulation may be made as equivalent to T. For purposes of such calculations with regard to testosterone esters, it is noted that 100 mg of T is equivalent to 139 mg testosterone enanthate, 158 mg testosterone undecanoate, 143 mg testosterone cypionate, and 183 mg testosterone palmitate. Amounts of therapeutic agents included in formulations of the invention may be proportionally adjusted, relative to testosterone.

[0056] The invention addresses the problem of providing an orally active androgen formulation that is well absorbed in the human body. It has been well established by dog (Shackelford J. Pharmacol. and Exp. Ther., 925-933, 2003) and human studies that testosterone undecanoate is absorbed almost exclusively via the intestinal lymphatics (Coert et al., Acta Endocrinol (Copenh), 789-800, 1975; Nieschlag et al., Acta Endocrinol (Copenh), 366-374, 1975; Horst et al., Klin Wochenschr, 875-879, 1976), thereby bypassing hepatic metabolism. Particularly, the invention provides SEDDS formulations of testosterone undecanoate containing phytosterols which enhances lymphatic absorption of TU by about 10% to about 300% over current commercial products, Andriol® Testocaps®, and known SEDDS formulations (U.S. Patent Application No. 2008/0317844; U.S. Patent Application No. 2010/0173882). The invention also provides a formulation of TU and/or testosterone that has a higher strength than currently known TU formulations. In one embodiment, the composition is formulated for parenteral

administration. In a further embodiment, the parenteral administration is intramuscular. One embodiment of the present invention also contemplates a formulation that releases the therapeutic agent into the patient's system at physiologically effective levels, over a period of up to 12 hours. Preferably, the formulation releases the therapeutic agent into the patient's system at physiologically effective levels over a period of up to 24 hours.

[0057] The invention provides embodiments where the formulation is effective for any of immediate release of the therapeutic agent, sustained release of the therapeutic agent, delayed release of the therapeutic agent, and/or any other modified release of the therapeutic agent. In one embodiment the invention provides a composition formulated for a combination of immediate and modified release of testosterone and/or testosterone esters.

[0058] The oral administration of hormones such as testosterone or estrogen has proven challenging. Testosterone is generally administered by oral ingestion in a bonded form as testosterone undecanoate, methyltestosterone, or testosterone cyclodextrin complex, to avoid the first pass effect. When administered in a regimen of hormone replacement therapy, it is desired to have sustained release properties, yet these forms of testosterone must be taken multiple times daily.

[0059] It was a general belief that testosterone itself could not be administered by oral ingestion. According to *The Pharmacological Basis of Therapeutics*, 10th ed., by Goodman and Gilman, oral administration of testosterone leads to absorption into the hepatic circulation but results in rapid metabolism by the liver. Therefore, oral ingestion is ineffective in delivering testosterone systemically. However, some researchers have further investigated oral administration of testosterone.

[0060] Svend Johnsen et al., in the publication entitled "Therapeutic Effectiveness of Oral Testosterone," (Johnsen et al., *Lancet*, 1974, 21; 2(7895):1473-5) described an oral administration of 200 mg of micronized testosterone, with a particle size in the range of 2 to 5 microns, to four patients with no testicular function. It was found that, for a period of about 5 to 7 hours, the total serum testosterone of the patient was in the range of about 300 to 900 ng/dL. Johnsen et al. recommended 200 mg testosterone administered twice daily. However, Johnsen et al. failed to address improving the pharmacokinetic properties of testosterone in order to administer the dose only once a day.

[0061] Marie Føgh et al., in the publication entitled "Serum-Testosterone During Oral Administration of Testosterone in Hypogonadal Men and Transsexual Women," (Føgh et al., *Acta. Endocrinol. (Copenhagen)*, 1978, 87(3): 643-9) described an oral administration of 200 mg of micronized testosterone twice daily. The two doses provided total serum testosterone within the normal range for greater than about 12 hours. A single 200 mg dose of orally administered testosterone with a particle size in the range of about 125-400 microns provided a total serum testosterone in the normal range for from about 5 to 7 hours. In view of the large doses required to maintain the desired serum levels of testosterone, and the possible side effects of such doses, Føgh et al. recommended not administering testosterone orally.

[0062] P. R. Daggett et al., in the article entitled "Oral Testosterone, a Reappraisal," (Daggett, et al., *Horm Res*. 1978, 9(3):121-9) described an oral administration of 200 mg of micronized testosterone twice daily. The dosage provided a double peak effect, with a desired level of serum testosterone

for about 4 hours for each peak. Daggett et al. found that the administration of oral testosterone was "unsuitable for routine use."

[0063] Nieschlag et al., in the publication entitled "Influence of Sex, Testicular Development and Liver Function on the Bioavailability of Oral Testosterone," (Nieschlag et al., *Eur. J. Clin. Invest.* 1977, 7(2):145-7) described orally administering 63 mg of testosterone in arachis oil to hypogonadal men. The serum level of testosterone rose to the desired level for a period of about 1 to 2 hours. Nieschlag et al. stated that oral testosterone "should be considered with caution, since higher testosterone doses would be needed to exceed the developing capacity of the liver to metabolize testosterone."

[0064] In the context of a general consensus that testosterone cannot be efficaciously orally administered, none of the above references discusses the possibility of providing sustained release properties or combining testosterone with a testosterone ester to modulate the release profile.

[0065] "Modified release," as used herein, generally refers to release of a drug that differs from immediate release of the drug under the same conditions via the same route of administration. Modified release may include each of immediate release, sustained release and delayed release. "Sustained release," as used herein, generally refers to release of a drug whereby the level of drug available to the patient is maintained at some level over a desired period of time. A variety of methods and formulations are used to provide sustained release of drugs. U.S. Pat. No. 5,567,439, describing methods of sustained release, is hereby incorporated by reference.

[0066] In one embodiment of the invention, the desired resulting level of total serum testosterone in a subject is in the range of from about 300 to about 1100 ng/dL in a male subject and in the range of from about 30 to about 110 ng/dL in a female subject. A formulation of the present invention, with testosterone or TU as the therapeutic agent delivers the desired level of serum testosterone for a minimum time period of about 8 to about 12 hours. After administration of a formulation of the invention with testosterone or TU as the therapeutic agent, the desired level of serum testosterone may be maintained for more than 12 hours. In a further embodiment the desired level of serum testosterone may be maintained for about 24 hours.

[0067] In exemplary formulations of the invention, the formulation is designed for administration three times a day (tid), two times a day (bid), or once a day (qd). Administration of a formulation of the invention may be by any regimen that achieves the desired resulting level of total serum testosterone in the target subject.

[0068] The formulation and methods of the present invention provide the ability to administer testosterone and/or testosterone ester in combination with sterols and/or sterol esters to achieve improved sustained release properties, as described more fully herein. In one embodiment, the administration is oral delivery. In other embodiments, the administration is parenteral, transdermal, nasal, sublingual, buccal or subcutaneous.

[0069] While various embodiments herein describe oral delivery of formulations and pharmaceutical compositions containing the therapeutic agent, it is further envisioned that the delivery of the drug is performed by any suitable delivery mechanism that provides therapeutically effective levels of the therapeutic agent. Other delivery routes that are compatible with the selected therapeutic agent and sterols or sterol esters are also contemplated as within the invention. Accord-

ingly, delivery methods of formulations or pharmaceutical compositions described herein include, but are not limited to sublingual administration, buccal administration, parenteral administration, intraperitoneal (i.p.) administration, intravenous (i.v.) administration, intraarterial (i.a.) administration, topical administration, transdermal administration, intradermal (i.d.) administration, intramuscular (i.m.) administration, subcutaneous (sc) administration, and nasal administration.

[0070] In a further embodiment the invention provides a formulation including more than one therapeutic agent. Where a second therapeutic agent is included in a formulation of the invention, the weight ratio of the primary therapeutic agent to the secondary therapeutic agent may be varied and will depend upon the effective dose of each ingredient. Each therapeutic agent contained in the composition or dosage form will be present in a therapeutically effective amount.

[0071] As described in detail above, the low bioavailability of a therapeutic agent caused by the high first-pass effect in the liver can be reduced by optimizing lymphatic absorption of the therapeutic agent. The present invention enables enhancement of the lymphatic absorption of testosterone esters and/or a combination of testosterone with testosterone esters, by formulations including sterols. In one embodiment, the sterols are phytosterols. It is shown herein that sterols, phytosterols and/or phytosterol esters modulate the solubility, stability, absorption, metabolism and pharmacokinetic profile of therapeutic agents that are lipophilic.

[0072] In another embodiment, the invention provides a formulation for the administration of a therapeutic agent in which the formulation contains a sterol in addition to the therapeutic agent, to provide desired properties of solubility, stability, absorption, metabolism and/or pharmacokinetic profile of the therapeutic agent. In a particular embodiment, the therapeutic agent is selected from testosterone and testosterone undecanoate.

[0073] As used herein, “stability” includes the stability of both the formulation and the therapeutic agent, both prior to administration and after administration to an individual. An improved stability prior to administration enables longer shelf life, less protective packaging, or storage at more aggressive environments. An improved stability after administration enables improved pharmacokinetic properties, such as higher exposure, or longer duration of action.

[0074] “Sterols,” as used herein, include all of plant, animal and fungal sterols. The sterols may be pure or may be a mixture of sterols. In one embodiment, the sterol is cholesterol. In another embodiment, the sterol is a “phytosterol,” a plant sterol or stanol, used herein to refer generally to plant-derived sterols or plant-derived stanols, phytochemicals that are added to foods, or supplements. Use of the term sterols also includes sterol esters, of any of plant-derived, animal-derived or fungal-derived sterol. “Sterol esters,” as used herein refer to plant sterols or stanols that have been esterified by creating an ester bond between a fatty acid and the sterol or stanol. Fatty acids used in esterification are plant-derived, animal-derived or fungal-derived. Esterification occurs in intestinal cells and is also an industrial process. Esterification may make plant sterols and stanols more fat-soluble so they are easily incorporated into fat-containing foods, including margarines and salad dressings. Exemplary sterols useful in the invention may include, but are not limited to, phytosterols, cholesterol, beta-sitosterol, and/or sitostanol.

[0075] Prior to the present invention, it was well known that a fed state or a fasting state of the subject could severely

interfere with the delivery of a therapeutic agent to that subject. As described above, the interactions between food and drugs should be individually evaluated.

[0076] The pioneering work of Borgstrom et al. (*J. Clin Invest*; 36:1521-1529, 1957) and Carey et al. (*Am J Med*; 49:590-598, 1970), as well as many others, contributed to the finding that the bile acid mixed micelle (BAMM) in the fed state and the bile acid (BA) micelle in the fasted state constitute the endogenous surfactant system that is responsible for the delivery or presentation of extremely lipophilic drugs to the enterocyte brush border region.

[0077] Cholesterol with a ClogP (calculated logP) of 12 and a water solubility of ~10 ng/mL is efficiently absorbed from the intestine by presentation of cholesterol dissolved in the BAMM droplets to the enterocyte brush border mucosa with subsequent collisional transfer to the glycocalyx. Many other extremely insoluble and lipophilic compounds are absorbed more efficiently in the fed state where the BAMM is present. The BAMM system is more effective than the BA system because of the higher micellar concentration in the fed as compared to the fasted state. The plant phytosterols which are present in food have similar ClogP and solubility but are slightly different in structure of the side chain and displace a significant percentage of cholesterol from the BAMM and reduce cholesterol absorption.

[0078] Accordingly, the present inventor selected sterols for investigation as providing a modulating effect on the solubility, stability, absorption, metabolism and/or PK profile of various lipophilic drugs. The modulating effect provided by sterols in formulations and methods of the invention is dependent upon the concentration of the sterols. In a particular embodiment the sterols are phytosterols dissolved in a formulation and/or co-dosed as a solid with a formulation. Since phytosterols are very lipophilic in nature (logP=12), high concentration of phytosterols suspended in lipid-based formulations bind strongly to the lipophilic drugs making the drug insoluble and unavailable for absorption. However, phytosterols dissolved in the lipid-based formulation to saturation (about 1% to about 20%) increase the solubility of the lipophilic drug, and increase bioavailability. (Tables 1-20 and FIGS. 5 and 6).

[0079] In food effect studies done to date and guidance issued by regulatory agencies, the fat content of the diet and its influence on the drug absorption has been emphasized. No attention has been given to the types of fat (saturated, monounsaturated, polyunsaturated, etc.) and the amount of cholesterol or plant sterols present in each meal. The vegetable oils contain a number of sterols that differ from cholesterol by having ethyl or methyl groups or unsaturation in the side chain. The predominant ones—sitosterol, stigmasterol, and campesterol—can be present in Western diets in amounts almost equal to dietary cholesterol (Miettinen T A, Tilvis R S, Kesäniemi Y A. *Am J. Epidemiol.* 1990; 131:20-31). The most prominent is β -sitosterol, which differs from cholesterol in that it has an ethyl group at carbon 24 of the side chain. In the early 1950s it was noted that the addition of sitosterol to the diet of cholesterol-fed chickens or rabbits lowered cholesterol levels in both species and inhibited atherogenesis in the latter (Pollak O J, Kritchevsky D. *Monogr Atherosclerosis*, 1981; 10:1-219). Sitosterol or mixtures of soy sterols were studied extensively as cholesterol-lowering agents between 1950 and 1960 (Lees A M, Mok H Y I, Lees R S, McCluskey M A, Grundy S M. *Atherosclerosis*, 1977; 28:325-338). The preparations achieved cholesterol

lowering of approximately 10% (Vahouny G V, Kritchevsky D. In: Spiller G A, ed. *Nutritional Pharmacology*. New York, N.Y.: Alan R Liss Inc; 1981:31-72.). The mode of action appears to involve inhibition of cholesterol absorption, although the plant sterols themselves are absorbed very poorly (Tilvis R S, Miettinen T A. *Am J Clin Nutr.*, 1986; 43:92-97). The mechanism of inhibition of cholesterol absorption is believed to be through crystallization and coprecipitation. Ingestion of 1 g of β -sitosterol reduced absorption of cholesterol by 42% in a meal containing 500 mg of cholesterol (Mattson F H, Grundy S M, Crouse J R. *Am J Clin Nutr.*, 1982; 35:697-700). The decrease in plasma cholesterol is probably due to an increase in LDL receptor activity. However, the decline in plasma cholesterol is relatively less than the decrease in absorption, presumably because of a compensatory increase in cholesterol synthesis.

[0080] In the 1980s it was demonstrated that sitostanol, a 5- α saturated sitosterol derivative, reduced the intestinal absorption of cholesterol and serum cholesterol more effectively than sitosterol and at doses below those of sitosterol. (Heinemann T, Leiss O, von Bergmann K., *Atherosclerosis*, 1986; 61:219-223). In a recent study (Miettinen T A, Puska P, Gylling H, Vanhanen H, Vartiainen E., *New Eng. J. Med.*, 1995; 333:1308-1312) sitostanol was interesterified with margarine, and the resultant product (1.9 to 2.6 g sitosterol per day) exhibited a hypocholesterolemic effect in a population with mild hypercholesterolemia. The mean 1-year reduction in plasma cholesterol was 10.2%. The sitostanol was not absorbed and did not appear to interfere with absorption of fat-soluble vitamins.

[0081] Phytosterols have a long history of safe use in humans. The drug Cytellin® was marketed in the United States between 1954 and 1982. The dosage was 6-18 g/d, with higher dosages recommended for those patients not responding to the standard dose. Dosages as high as 45 g/d were reported to be well tolerated without serious side effects (Eli Lilly Package Insert M100 Suspension Cytellin® (Beta and Di-hydrobeta sitosterols). A drug product indicated for the reduction of hypercholesterolemia. Dated 1954.). In the modern era, phytosterols have been used as margarine additives since about 1995, with the introduction of stanol esters to the Finnish market, and in 2000 with the introduction of sterol esters under Novel Foods regulations in the EU. As a requirement for market approval, post-launch monitoring was conducted in the EU, with no unpredicted side effects reported (Lea L J, Hepburn P A. Safety evaluation of phytosterol esters. Part 9: Results of a European post-launch monitoring programme. *Food Chem. Toxicol.*, 2006; 44:1213-22.). The recommended plant sterol/stanol dosages for margarine and other foods are relatively low compared with that of Cytellin®. Consumption levels of 400 mg twice daily of phytosterols are now recommended. (Press release dated Feb. 24, 2003 at World Wide Web address: npicenter.com/ann/templates/newsATemp.aspx?articleid=4011&zoneid=3).

[0082] The principal (n-3) long-chain polyunsaturated fatty acids (LCPUFA) in marine oils, eicosapentanoic acid (EPA; 22:5(n-3)) and docosahexanoic acid (DHA; 22:6(n-3)), have been shown to possess a wide range of physiological effects, from alterations in circulating plasma lipids to eicosanoid and cytokine production. There is considerable evidence to support reductions in triglycerides and improvement in circulating HDL-cholesterol in response to high dosage (1-5 gm/d) (n-3) LCPUFA oil supplementation.

[0083] In a recent clinical study, it was found that combined supplementation of (n-3) LCPUFA (1.4 g/d) as oils with phytosterols (2 g/d) has both synergistic and complementary lipid-lowering effects in hyperlipidemic men and women. The combination of phytosterols and (n-3) LCPUFA has been shown to reduce plasma total cholesterol by 13.3% and LDL-cholesterol by 12.5%. The HDL-cholesterol concentration was increased by (n-3) LCPUFA (7.1%) alone and in combination with phytosterols (8.6%), whereas phytosterol treatment alone had no effect. Plasma triglyceride concentration was lowered by (n-3) LCPUFA (22.3%) alone and in combination with phytosterols (25.9%), whereas phytosterol treatment alone had no effect. (Michelle A. Micallef et al., *J. Nutr.* 138: 1086-90, 2008)

[0084] Testosterone is implicated as one of the gender-related risk factors for coronary artery disease in men due to its HDL-C lowering effect. Weekly administration of 200 mg TE to male powerlifters decreased HDL-C and apolipoprotein A significantly but total cholesterol, LDL-C or triglyceride levels were not altered (Zmuda et al, *Metabolism* 42: 446-450, 1993).

[0085] In a further embodiment, testosterone and/or testosterone ester formulations of the present invention containing LCPUFA and phytosterols may be used to minimize the HDL-C lowering effect observed with currently available testosterone and/or testosterone ester products delivered via oral, parenteral, intramuscular, transdermal, nasal, sublingual, buccal and/or subcutaneous routes of administration.

[0086] In one embodiment, the invention provides a formulation for the oral administration of a therapeutic agent which contains testosterone, testosterone undecanoate and/or another testosterone ester in combination with a phytosterol, where the phytosterol provides modulation of one or more of: solubility, stability, absorption, metabolism and pharmacokinetic profile of the testosterone or testosterone ester. The concentration of the dissolved phytosterol(s) ranges from about 1% to about 30% of the formulation, preferably about 2% to about 20% solubilized in the formulation to exhibit the desired modulating effect.

[0087] In another embodiment, the formulation further comprises LCPUFA, LCPUFA oils, LCPUFA esters, and mixtures thereof in addition to the phytosterol and therapeutic agent.

[0088] In yet another embodiment, the formulation further comprises solubilizers (lipids, surfactants, etc.), and LCPUFA, LCPUFA oils, LCPUFA esters, and mixtures thereof, in addition to the phytosterol and therapeutic agent.

[0089] In one embodiment, the amount of phytosterol and/or phytosterol esters in the formulation is an amount effective to modulate the solubility, stability, metabolism and/or bioavailability to deliver the desired PK profile for a minimum of about 8 to about 12 hours. In another embodiment, the modulation will last longer than 12 hours, preferably about 24 hours. This modulative effect is important for hormone replacement therapies, e.g., in elderly men with partial androgen deficiency (PADAM patients), in that a deficient plasma level of testosterone can be appropriately corrected.

[0090] Another embodiment of a dosing regimen for hormone replacement therapy (HRT) involves administering orally a testosterone and/or testosterone ester formulation to hypogonadal men for a specified duration (1 week to 6 months) to achieve normal physiological levels of testosterone (300 ng/dL-1100 ng/dL in a male subject), followed by

parenteral administration of a long acting intramuscular product of the present invention every (6-12 weeks) for maintenance therapy.

[0091] As described in detail above, sustained solubilization is a desirable characteristic in formulations for enhancing the bioavailability of water insoluble, lipophilic drugs. In one embodiment, the invention includes formulations including a therapeutic agent, a sterol and a non-sterol solubilizing agent for solubilization of the therapeutic agent. As such, absorption is not dependent on the dissolution of the therapeutic agent from the formulation in the patient's gastrointestinal tract, as all or a substantial fraction of the therapeutic agent in the formulation is already solubilized prior to administration to the patient, increasing the amount of therapeutic agent available for absorption. In a particular embodiment the therapeutic agent is selected from testosterone and testosterone undecanoate and the sterol is a phytosterol.

[0092] A "solubilizer" as referred to herein, may also be referred to as a "solubilizing agent." The terms are used interchangeably.

[0093] Solubilizers included in formulations of the invention are any pharmaceutically acceptable material that has a solubility for TU of at least about 1 mg per gram of the solubilizer, more preferably at least about 40 mg per gram of the solubilizer, and most preferably at least about 100 mg per gram of the solubilizer. The solubilizer is preferably present in an amount such that a significant fraction of the therapeutic agent is solubilized in the composition and is capable of providing an immediate and therapeutically effective amount of the therapeutic agent to a patient in a readily absorbable form upon administration. In one embodiment, the therapeutic agent is testosterone undecanoate, which provides a therapeutically effective amount of testosterone to a patient. Preferably, the solubilizers of the present invention can also increase the solubilization of TU or any other therapeutic agent when the composition contacts an aqueous medium, and particularly gastro-intestinal fluids upon administration of the dosage form containing the composition. Thus, the solubilizers as provided herein improve the dissolution profile of TU or any other therapeutic agent and thereby the bioavailability of TU or any other therapeutic agent. In various embodiments, the solubilizer is a non-sterol solubilizer.

[0094] In one embodiment, the solubilizers are selected from triglycerides, diglycerides, monoglycerides, free fatty acids, and fatty acid esters and derivatives thereof, individually or in combination. Examples of solubilizers include, but are not limited to, propylene glycol dicaprylate/caprate, caprylic/capric triglyceride, caprylic/capric/linoleic triglyceride, e.g. synthetic medium chain triglycerides having C₈₋₁₂ fatty acid chains or other derivatized (synthetic) triglycerides of the type known and commercially available under Miglyol 810, 812, 818, 829 and 840, linoleic acid, linoleic acid ethyl ester, fish oils as free fatty acids, their esterification and their transesterification products, e.g., of the type known and commercially available under EPAX 6000 FA, EPAX 4510 TG, individually or in combination. Additional examples include vegetable oils and C₁₂₋₁₈ fatty acid mono-, di- and triglycerides prepared by individual admixing or as transesterification products of vegetable oils (such as soybean oil, almond oil, sunflower oil, olive oil or corn oil) with glycerol. Particularly preferred lower alcohol fatty acid esters include ethyl oleate, ethyl linoleate, ethyl caprylate, ethyl caprate, isopropyl myristate, isopropyl palmitate and mixtures thereof.

[0095] In the art of pharmaceutical formulation, vitamin E substances have been known for their reducing potential and typically used as antioxidants in pharmaceutical compositions. The inventor has found, however, that vitamin E substances have unexpected solubilization power toward testosterone undecanoate and other hydrophobic therapeutic agents. Therefore, in one embodiment, the formulation includes a vitamin E solubilizer.

[0096] The inventor also has surprisingly found that nitrogen-containing solvents have unexpected solubilization power toward testosterone undecanoate and other hydrophobic therapeutic agents relative to other commonly used non-nitrogen containing solvents such as glycerol, propylene glycol, and polyethylene glycols. The nitrogen-containing solvent solubilizer may be selected from, but is not limited to: dimethylformamide, dimethylacetamide, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam and mixtures thereof wherein alkyl is a C₁₋₁₂ branched or straight chain alkyl. Particularly preferred nitrogen-containing solvents include N-methyl 2-pyrrolidone, N-ethyl 2-pyrrolidone or a mixture thereof. Alternatively, the nitrogen-containing solvent may be in the form of a polymer such as polyvinylpyrrolidone. In another embodiment, the formulation includes a solubilizer selected from nitrogen-containing solvents,

[0097] In additional research, the inventor has further surprisingly found that replacing one or more of the hydroxyl groups of glycerol and propylene glycol with, for example, a C₂-C₂₄ alkyl ester, results in a propylene glycol or glycerol fatty acid ester with an unexpectedly high solubilizing power for testosterone undecanoate. In another embodiment, the formulation includes a solubilizer selected from dehydroxylated, esterified non-nitrogen containing solvents, where the hydroxyl group has been replaced with an ester.

[0098] Similarly, additional research has yielded other unexpectedly effective solubilizers for testosterone undecanoate, including esters of monohydric alcohols such as ethanol and ethylene glycols such as polyethylene glycols, with an organic acid such as acetic acid, fatty acids and citric acids.

[0099] Another group of solubilizers for use in formulations of the invention includes phospholipids. Solubilizing phospholipids include, but are not limited to, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, lecithins, lysolecithins, lysophosphatidylcholine, polyethylene glycolated phospholipids/lysophospholipids, lecithins/lysolecithins and mixtures thereof.

[0100] In still another embodiment, a formulation of the invention contains a solubilizer that is a hydrophobic or hydrophilic surfactant that would enhance the galenic properties of the therapeutic agent within the formulation. Examples of suitable surfactants include, but are not limited to: polyoxyethylene-sorbitan-fatty acid esters; e.g., mono- and tri-lauryl, palmityl, stearyl and oleyl esters; e.g., products of the type known as polysorbates and commercially available under the trade name Tween®; polyoxyethylene fatty acid esters, e.g., polyoxyethylene stearic acid esters of the type known and commercially available under the trade name Myrj®; polyoxyethylene castor oil derivatives, e.g., products of the type known and commercially available as Cremophors®. Particularly suitable are polyoxyl 35 castor oil (Cremophor®EL) and polyoxyl 40 hydrogenated castor oil (Cremophor®RH40); α -tocopherol, α -tocopheryl polyethylene glycol succinate (vitamin E TPGS), α -tocopherol palmi-

tate and α -tocopherol acetate; PEG glyceryl fatty acid esters such as PEG-8 glyceryl caprylate/caprinate (commercially known as Labrasol®), PEG-4 glyceryl caprylate/caprinate (Labrafac® Hydro WL 1219), PEG-32 glyceryl laurate (Gelucire® 44/14), PEG-6 glyceryl mono oleate (Labrafil® M 1944 CS), PEG-6 glyceryl linoleate (Labrafil® M 2125 CS); propylene glycol mono- and di-fatty acid esters, such as propylene glycol laurate, propylene glycol caprylate/caprinate; also diethyleneglycol-monoethylether (DGME), commercially known as Transcutol® (Gattefosse, Westwood, N.J.); sorbitan fatty acid esters, such as the type known and commercially available under the name Span® (e.g., Span 85); polyoxyethylene-polyoxypropylene co-polymers, e.g., products of the type known and commercially available as Pluronic® or Poloxamer®; glycerol triacetate; and monoglycerides and acetylated monoglycerides, e.g., glycerol monodicoate (Imwitor® 928), glycerol monocaprylate (Imwitor® 308), and mono- and di-acetylated monoglycerides.

[0101] As described in detail above, one widely utilized approach to achieve sustained solubilization is to utilize formulations within a lipid vehicle containing surfactants that constitute a SEDDS or SMEDDS, to effect spontaneous emulsification upon contact of the lipid with fluids in the GI tract.

[0102] Hydrophilic-Lipophilic Balance (HLB) is a term used to describe an arbitrary scale from 0 to 40 depicting the Hydrophilic/Lipophilic Balance of a surfactant. Products with low HLB are more oil soluble. High HLB represents good water solubility. HLB is a numerically calculated number based on the surfactants' molecular structure. It is not a measured parameter.

[0103] An optimal surfactant hydrophilic lipophilic balance (HLB) for emulsification was found to be around 10 (Shah, N. H. et. al., *Int. J. of Pharmaceutics*, 106 (1994) 15-23), which can be achieved using a combination of polar and non-polar surfactants. Polar surfactants with high HLB's have been utilized to enable microemulsion formation, while inclusion of a non-polar surfactant (HLB<8) such as medium chain mono/diglycerides can also improve miscibility with oils. These pre-concentrates can be administered in softgels, hardgels, or adsorbed on to inert inorganic or organic polymers to generate free flowing powders. The powder can be compressed into tablets, filled into hard gelatin capsules or formulated into other oral dosage forms known to the art. Alternatively, the pre-concentrates can be formulated for parenteral, intramuscular, transdermal, nasal, sublingual, buccal and subcutaneous administration.

[0104] As described herein, formulations containing solubilizers enhance bioavailability of the therapeutic agent by their solubilization action. Under fasted conditions, a solubilizing species present in the intestinal contents comprise low concentrations of bile salt, phospholipids and cholesterol derived from fasted biliary output. In the absence of exogenous lipids the solubilization capacity of the fasted small intestine remains low and is correlated with the total bile salt concentrations rather than reflecting the structure of the individual colloidal species (Pendersen et al., *Pharm Res.* 17, 891-894, 2000; Kaukonen et al., *Pharm Res.* 21, 245-253, 2004). Following the addition of lipids that are representative of the digestion products of exogenously derived (from lipid-based formulation or food) lipids, the drug solubilization capacity increases significantly and is dependent on the nature of the digestion products (in terms of the fatty-acid

chain length) and the characteristics of the colloidal structures they form. For example, the digestion products of medium-chain triglycerides (C_8 - C_{12} fatty acids and monoglycerides) are amphiphilic and readily combine with endogenous bile salt, phospholipid and cholesterol to provide highly dispersed, optically clear dispersions (even at high (~150 mM) lipid loads). The drug solubilization capacity of these composite colloidal species can be up to 50-fold higher than that of endogenous bile salt, phospholipids and cholesterol species (Kosenna et al., *J. Pharm. Sci.* 93, 332-348, 2004).

[0105] However, the solubilization capacity is dependent on lipid concentration, and the solubility of a range of poorly water-soluble drugs has been shown to be enhanced by less than threefold at lower (<25 mM) exogenous lipid levels (Kosenna et al., *J. Pharm. Sci.* 93, 332-348, 2004; Kosenna et al., *J. Pharm. Sci.* 94, 481-492, 2005). By contrast, the phase behavior and solubilization characteristics of the species formed on the intercalations of the digestion products of long-chain triglycerides (which comprise primarily C_{18} lipids, e.g. palm oil, corn oil, canola oil, soybean oil, olive oil, peanut oil, sesame oil, hydrogenated vegetable oils, hydrogenated soybean oil, etc.) vary significantly when compared to medium-chain triglycerides (Kosenna et al., *J. Pharm. Sci.* 94, 481-492, 2005). C_{18} fatty acids and monoglycerides are considerably less polar than their C_8 or C_{12} equivalents and turbid systems that contain larger (~100 nm) vesicular species are evident even at low (>2.5 mM) lipid concentrations. Importantly, these vesicular species provide for significantly enhanced drug solubilization capacities. For example, in the presence of 8.75 mM long-chain fatty acids and 4.4 mM long-chain monoglycerides (approximately the same mass per mass quantities of lipid that led to a less than a threefold improvement in solubilization capacity for medium-chain lipids) solubilization enhancements of up to 20-fold are apparent (Kosenna et al., *J. Pharm. Sci.* 93, 332-348, 2004; Kosenna et al., *J. Pharm. Sci.* 94, 481-492, 2005). These solubilization differences, which are based on lipid content, are particularly significant in the context of the likely luminal concentration of lipid obtained after oral administration of a lipid-based formulation. For example, assuming a lipid dose of 750 mg long-chain triglyceride and complete digestion, the maximal luminal concentrations of fatty acid and monoglyceride (solubilized in micelles) post-digestion are approximately 8.5 mM and 4.2 mM, respectively.

[0106] In contrast to micronized testosterone compositions, the present formulations do not require a separate in vivo step for the dissolution of crystalline testosterone undecanoate since a significant fraction of TU is already solubilized in the compositions by the included solubilizer.

[0107] Accordingly, the invention in various embodiments provides a formulation for administration of a therapeutic agent, including 1) one or more lipophilic, poorly water soluble therapeutic agents, 2) a sterol or ester thereof; and 3) a solubilizing agent effective for solubilization of the therapeutic agent. In a particular embodiment, the therapeutic agent is an androgen, and in a more particular embodiment, the androgen is selected from testosterone and testosterone esters, such as testosterone undecanoate. In a preferred embodiment the sterol or ester thereof is a phytosterol. In another embodiment the solubilizing agent is a non-sterol solubilizing agent.

[0108] In another embodiment the invention provides a method of enhancing solubility of one or more poorly water

soluble therapeutic agents, including combining 1) a phytosterol or phytosterol ester, 2) a non-sterol solubilizing agent effective for solubilization of the therapeutic agent, and 3) at least one lipophilic, poorly water soluble therapeutic agent, to form a composition, wherein the composition is effective to enhance solubility of the at least one therapeutic agent, as compared to the solubility of the same therapeutic agent in the absence of 1) a phytosterol or phytosterol ester and 2) a non-sterol solubilizing agent effective for solubilization.

[0109] In other embodiments of the present invention, methods and compositions for enhancing the absorption and metabolic stability of testosterone or testosterone undecanoate by incorporating components that may biochemically modulate (1) T or TU absorption, (2) T or TU metabolism, and/or (3) metabolism of TU to DHTU. For example, TU is absorbed almost exclusively via the intestinal lymphatics (Coert et al., *Acta Endocrinol (Copenh)*, 789-800, 1975; Nieschlag et al., *Acta Endocrinol (Copenh)*, 366-374, 1975; Horst et al., *Klin Wochenschr*, 875-879, 1976; Shackelford J. *Pharmacol. and Exp. Ther.*, 925-933, 2003) thereby bypassing hepatic metabolism. Formulations containing oleic acid, glycerol monooleate, Polyoxyl 40 Hydrogenated Castor Oil (e.g., Cremophore RH 40), Polysorbate 80 (e.g., Tween 80), and phytosterols (Formulation #54) enhance lymphatic absorption relative to the Castor oil and Lauroyl glycol (Andriol Testocap®) formulation by 294%. Cremophore RH 40, Tween 80, and Solutol HS 15 are known Pgp efflux and P450 inhibitors. Tween 80 is also a known chylomicron secretion inducer. By using appropriate ratios of Cremophore RH 40, and Tween 80, metabolic stability and lymphatic absorption of TU can be enhanced to achieve the desired PK profile. In one embodiment the formulation contains Polyoxyl 40 Hydrogenated Castor Oil (e.g., Cremophore RH 40) and Polysorbate 80 (e.g., Tween 80) in a ratio of about 1:10 to about 10:1, more preferably about 1:2 to about 2:1.

[0110] Other components that can enhance TU absorption and metabolic stability include natural (e.g., phytosterols, borage oil, gamma-linoleic acid) and synthetic inhibitors (e.g., MK386) of 5- α -reductase absorbed via intestinal lymphatics. 5- α -reductase inhibitors such as finasteride and dutasteride have minimal effect on modulation of T or DHT exposure from oral T or T esters (Table 24) as they are absorbed via the portal vein.

[0111] The invention further provides a formulation for oral administration of a therapeutic agent, including 1) one or more lipophilic, poorly water soluble therapeutic agents, 2) a sterol or ester thereof; 3) a solubilizing agent effective for solubilization of the therapeutic agent; and 4) an enhancing agent. In a particular embodiment, the therapeutic agent is an androgen, and in a more particular embodiment, the androgen is selected from testosterone and testosterone esters, such as testosterone undecanoate. In a preferred embodiment the sterol or ester thereof is a phytosterol. In another embodiment the solubilizing agent is a non-sterol solubilizing agent. In a further embodiment the formulation comprises an enhancing agent. In a particular embodiment the enhancing agent is selected from the group consisting of: an inhibitor of 5- α -reductase enzymes, a P450 inhibitor, a Pgp inhibitor and a chylomicron secretion inducer. In a further embodiment the 5- α -reductase inhibitor is MK-386, phytosterols, borage oil, or gamma-linoleic acid; the P450 and/or Pgp inhibitors are selected from peppermint oil, Cremophore RH 40, Tween-80, and Solutol HS 15; and the chylomicron secretion inducer is Tween 80.

[0112] In another embodiment the invention provides a method of enhancing biological absorption and/or metabolic stability of one or more poorly water soluble therapeutic agents, including administering: 1) a sterol or ester thereof; 2) a non-sterol solubilizing agent effective for solubilization of the therapeutic agent; 3) an enhancing agent effective to improve the biological absorption and/or metabolic stability of at least one therapeutic agent; and 4) at least one lipophilic, poorly water soluble therapeutic agent, to form a composition, wherein the composition is effective to enhance biological absorption and/or metabolic stability of at least one therapeutic agent, as compared to correspondingly administered therapeutic in the absence of 1) a sterol or ester thereof; 2) a non-sterol solubilizing agent; and 3) an enhancing agent.

[0113] In a further embodiment the invention provides a formulation consisting essentially of a therapeutic agent and an enhancing agent effective to improve the biological absorption and/or metabolic stability of the therapeutic agent. In a particular embodiment the enhancing agent is selected from Cremophore RH 40, Tween-80, phytosterols and phytosterol esters.

[0114] The formulations of the invention make use of the advantages of oral administration of androgens, especially of testosterone and the esters thereof, by exploiting the different pharmacokinetics of the various testosterone esters in combination with phytosterols and/or phytosterol esters, so as to be able, by careful selection of appropriate dosages and esters, to attain a desired drug profile. Particularly, the invention is advantageous for administration of androgens having high first-pass effect and low bioavailability. Formulations of the invention may include further additives to achieve a cumulative or additional therapeutic effect.

[0115] Examples of such further additives may include, but are not limited to lipids, bile salts, 5- α -reductase inhibitors and any other additives effective in increasing the bioavailability of the therapeutic agent, maximizing absorption of the therapeutic agent, treating additional conditions and/or reducing side effects of drug administration, e.g. inflammation. Classes of additives that may be present in the compositions, include, but are not limited to, absorbents, acids, adjuvants, anticaking agent, glidants, antitackling agents, antifoamers, anticoagulants, antimicrobials, antioxidants, antiphlogistics, astringents, antiseptics, bases, binders, chelating agents, sequestrants, coagulants, coating agents, colorants, dyes, pigments, compatibilizers, complexing agents, softeners, crystal growth regulators, denaturants, desiccants, drying agents, dehydrating agents, diluents, dispersants, emollients, emulsifiers, encapsulants, enzymes, fillers, extenders, flavor masking agents, flavorants, fragrances, gelling agents, hardeners, stiffening agents, humectants, lubricants, moisturizers, bufferants, pH control agents, plasticizers, soothing agents, demulcents, retarding agents, spreading agents, stabilizers, suspending agents, sweeteners, disintegrants, thickening agents, consistency regulators, surfactants, opacifiers, polymers, preservatives, antigellants, rheology control agents, UV absorbers, tonicifiers and viscomodulators. The formulation may include one or more additives.

[0116] Examples of lipids that may be included as additives to a basic formulation of the invention include, but are not limited to essential fatty acids. Essential Fatty Acids (EFAs) are necessary fats that humans cannot synthesize, and must be obtained through diet. EFAs are long-chain polyunsaturated fatty acids derived from linolenic, linoleic, and oleic acids. There are two families of EFAs: omega-3 and omega-6.

Omega-9 is necessary yet “non-essential” because the body can manufacture a modest amount on its own, provided essential EFAs are present. The number following the “omega-” prefix represents the position of the first double bond, counting from the terminal methyl group on the molecule. Omega-3 fatty acids are derived from linolenic acid, omega-6 from linoleic acid, and omega-9 from oleic acid.

[0117] Alpha linolenic acid (ALA) is the principal omega-3 fatty acid, which a healthy human will convert into eicosapentaenoic acid (EPA), and later into docosahexaenoic acid (DHA). EPA and the gamma linolenic acid (GLA) synthesized from linoleic (omega-6) acid are later converted into hormone-like compounds known as eicosanoids, which aid in many bodily functions including vital organ function and intracellular activity. Linoleic acid is the primary omega-6 fatty acid. A healthy human with good nutrition will convert linoleic acid into GLA.

[0118] Therefore, in another embodiment, the formulation further includes one or more triglycerides containing fatty acids, including, but not limited to, omega-3, omega-6 and omega-9.

[0119] It is known that oral TU treatment elevates DHT, which may be associated with an increased risk of acne, male pattern baldness and prostate hyperplasia. Co-administration of a 5- α -reductase inhibitor, such as finasteride or dutasteride has been shown to prevent reduction of testosterone to DHT. Commercial preparations of finasteride and dutasteride are known, e.g. Proscar[®], Propecia[®], and Avodart[®].

[0120] As will be recognized by those skilled in the art, the amount or percentage of the therapeutic agent present in the formulation and dosage forms will vary. Thus, for example, the amount of therapeutic agent is based, in part, upon the actual need of the patient and can be determined by the attending clinician. In all cases, however, the amount of the therapeutic agent present in the composition and dosage forms is an amount such that the therapeutic agent is significantly solubilized in the appropriately selected solubilizer or solubilizers so that the aforementioned advantages of the present invention are achieved. In a particular embodiment the amount or percentage of all elements of a formulation of the invention are optimized to achieve a desired level of total serum testosterone in a subject in the range of from about 300 to about 1100 ng/dL in a male subject, and about 30 to about 110 ng/dL in a female subject, over a time period of about 8 hours to about 24 hours.

[0121] The terms “effective amount” or “therapeutically effective amount” as used herein refer to a nontoxic but sufficient amount of the therapeutic agent to provide the desired therapeutic effect within a subject. The exact amount that is “effective” will vary from subject to subject, depending on the age, weight and general condition of the subject, the severity of the condition being treated, the judgment of the clinician, and the like. However, an appropriate “effective amount” in any individual case can be determined by one of ordinary skill in the art using only routine experimentation, based on the disclosure herein.

[0122] Preferably, the formulations are prepared so as to contain a sufficient amount, i.e., dose of TU within a dosage unit, e.g., a capsule. It is preferred that the amount of testosterone will be present in the formulation so as to provide each dosage form with a unit dosage of from about 1 to about 1000 mg, and preferably about 40 to about 400 mg of testosterone undecanoate for oral administration, and preferably from 200 to 1000 mg for parenteral. Typically the testosterone

and/or testosterone ester is from about 0.1% to about 80% of the formulation by weight. Preferably, the testosterone and/or testosterone ester is from about 0.1% to about 50% of the formulation by weight. More preferably, the testosterone and/or testosterone ester is from about 0.1% to about 40% of the formulation by weight. In various other embodiments, the testosterone and/or testosterone ester may be in a range having a lower value of any of 0.01, 0.05, 0.1, 0.15, 0.2, 0.5 and 1%, and having an upper value of any of 70.5, 71.0, 71.25, 71.5, 71.75, 72.0, 73.0, 74.0, 75.0, 77.5, 79.0, 79.5, 79.75, 79.9, 79.95 and 80.0%.

[0123] In one embodiment, it is particularly preferred that the entire amount of TU is solubilized in the composition. However, it is sometimes necessary to add additional TU in non-solubilized form when the TU solubility capacity of a given composition is exceeded. Therefore, it is also an important feature of the present invention that the TU present in the composition is significantly solubilized. Typically, at least about 20% of the TU is solubilized in the composition and preferably at least about 50% of the TU is solubilized in the composition of the dosage form. The dosage form contains TU solubilized in the composition in an amount of at least about 1 mg, preferably in an amount of at least about 40 mg, and more preferably in an amount of at least about 100 mg.

[0124] Although the formulation may be administered to a subject in any suitable dosage form, the dosage form is preferably a capsule or other oral dose form (e.g., a tablet, lozenge, etc.) containing the formulation having a therapeutically effective amount of testosterone and/or testosterone undecanoate contained therein. In an additional embodiment, the dosage form is preferably a formulation suitable for parenteral administration, e.g. an intra-muscular injection.

[0125] The amount of solubilizer that can be included in a formulation of the present invention is not particularly limited. When the formulation is administered to a subject, however, the amount of any given solubilizer is limited to a bio-acceptable amount. Bio-acceptable amounts of solubilizers and other components are readily determined by one of skill in the art by using routine experimentation or searching the literature. In some circumstances, it may be advantageous to include amounts of solubilizers far in excess of bio-acceptable amounts, for example, to maximize the concentration of the TU, with excess solubilizer removed prior to providing the composition to a patient. Excess solubilizer may be removed using conventional techniques such as distillation, spray drying, lyophilization or evaporation. Generally, the amount of solubilizer in the composition will be from about 10% to about 90%, preferably between about 12.5% to about 85% by weight. In various other embodiments, the solubilizer may be in a range having a lower value of any of 0.01, 9.05, 9.1, 9.15, 9.2, 9.5 and 10%, and having an upper value of any of 80.5, 81.0, 81.25, 81.5, 81.75, 82.0, 83.0, 84.0, 85.0, 87.5, 89.0, 89.5, 89.75, 89.9, 89.95 and 90.0%.

[0126] In one embodiment, the formulation also contains 1% to 99% by weight of a sterol and/or sterol ester. In a preferred embodiment the formulation contains about 1% to about 90% of phytosterol and/or phytosterol esters, solubilized and/or suspended. Preferably, the formulation contains from about 1% to about 70% of phytosterols and/or phytosterol esters; more preferably, the formulation contains from about 1% to about 45% of phytosterols and/or phytosterol esters. In a more preferred embodiment, the formulation contains about 2% to about 20% solubilized phytosterols or phytosterol esters. In a further embodiment, additional

phytosterols or phytosterol esters may be co-dosed with a formulation of the invention. In various other embodiments, the total phytosterol and/or phytosterol esters, solubilized and/or suspended may be in a range having a lower value of any of 0.01, 0.05, 0.1, 0.15, 0.2, 0.5 and 1%, and having an upper value of any of 80.5, 81.0, 81.25, 81.5, 81.75, 82.0, 83.0, 84.0, 85.0, 87.5, 89.0, 89.5, 89.75, 89.9, 89.95 and 90.0%.

[0127] In a further embodiment of the invention, phytosterols or phytosterol esters may be added with the therapeutic agent in solubilized form, in suspended form, as an additive, as a co-dose accompanying dosing of a formulation of the invention, or any combination thereof.

[0128] The amount of additional components in a formulation of the invention can be determined by one of ordinary skill in the art, according to the desired property or properties to be imparted to the composition. For example, the amount of a suspending agent may be determined by adding gradual amounts of the agent until the desired homogeneity of undissolved drug particles in the composition is achieved. For a colorant, the amount of the colorant may be determined by adding small amounts of the colorant until the desired color of the composition is achieved. For a surfactant, the amount of a surfactant may be determined by adding gradual amounts of the surfactant until the desired wetting effect or dispersibility of the composition is achieved. The amount of surfactant, when present, in the composition will generally be up to about 80 wt. %, preferably between about 1 wt. % to about 50 wt. %, more preferably between 1 wt. % to about 35 wt. %.

[0129] In a particular embodiment, the invention provides a formulation containing a therapeutically effective amount of a hydrophobic drug, a phytosterol and/or phytosterol ester, and a LCPUFA, LCPUFA oils, LCPUFA esters or mixtures thereof. The hydrophobic drug is present in an amount of from about 0.1 to 70% w/w of the composition. Furthermore, the hydrophobic drug is at least about 20% solubilized in the composition. The LCPUFA substance in the composition is present in an amount of from about 1 to 99% w/w of said composition. The phytosterols and/or phytosterol esters are suspended in the formulation in an amount of from 1% to 40%.

[0130] In a further embodiment, a formulation of the invention may be provided as a pharmaceutical composition. As such, the formulation is provided in a dosage form, for administration to a subject in need of such formulation.

[0131] Administration of a formulation of the invention may be as a single composition, or as multiple compositions. The formulations and compositions thereof may be administered at the same time or may be administered at different times. Administration may be performed by any method which results in the desired serum concentration of therapeutic agent.

[0132] In a preferred embodiment, the pharmaceutical composition is present in a single dosage form. The dosage form(s) are not limited with respect to size, shape or general configuration, and may comprise, for example, a capsule, a tablet or a caplet, or a plurality of granules, beads, powders or pellets that may or may not be encapsulated. A preferred dosage form is a capsule containing a composition as described herein (FIG. 1). The capsule material may be either hard or soft and is generally made of a suitable compound such as gelatin, starch or a cellulosic material. As is known in the art, use of soft gelatin capsules places a number of limitations on the compositions that can be encapsulated. See, for

example, Ebert (1978), "Soft Elastic Gelatin Capsules: A Unique Dosage Form," *Pharmaceutical Technology* 1(5). Two-piece hard gelatin capsules are preferably sealed, such as with gelatin bands or the like. See, for example, *Remington: The Science and Practice of Pharmacy*, Twenty first Edition. (2006) cited supra, which describes materials and methods for preparing encapsulated pharmaceuticals. In this embodiment, the encapsulated composition may be liquid or semi-solid (e.g., a gel).

[0133] The formulation may optionally include a carrier, in addition to the therapeutic agent, sterol and solubilizer. In one embodiment, the carrier contains the solubilizer. In one embodiment, the carrier includes one or more solubilizers and, optionally further includes one or more pharmaceutically acceptable additives in addition to the solubilizer.

[0134] "Carrier" or "vehicle" as used herein refers to carrier materials suitable for drug administration. Carriers and vehicles useful herein include any such materials known in the art, e.g., any liquid, gel, solvent, liquid diluent, solubilizer, surfactant, or the like, which is nontoxic and which does not interact with other components of the composition in a deleterious manner.

[0135] In one embodiment of the invention, the formulation is provided in a lipid suspension as a pharmaceutical composition.

[0136] The lipids may be of animal, vegetable or mineral origin, which are substantially water-insoluble, inert, non-toxic hydrocarbon fats and oils and derivatives thereof, and may comprise any of the commonly commercially available fats or oils approved by the Food & Drug Administration. The lipid may be a liquid or a solid at room temperature. Preferably, the lipid has a melting point in the range of about 90 to 160° F. (32 to 71° C.). The lipid may comprise a vegetable oil base commonly known as hard butter. Hard butters are hydrogenated, press fractionated, or other processed oils that are processed or recombined to have a solid fat index (percent solid fat vs. temperature) similar to that of cocoa butter. However, other lipids may be used that are relatively hard or solid at room temperature, but melt rapidly in the mouth at a temperature of about 92° to 98° F. (29 to 32° C.). The lipid is employed in the amounts within the range of from about 20 to about 50%. Examples of suitable lipids include tallow, hydrogenated tallow, hydrogenated vegetable oil, almond oil, coconut oil, corn oil, cottonseed oil, fish oil, light liquid petrolatum, heavy liquid petrolatum, olein, olive oil, palm oil, peanut oil, persic oil, sesame oil, soybean oil, castor oil or safflower oil.

[0137] Additionally, stearines can be used as a lipid in the present invention. The addition of stearines to the product provides the favorable property of mold-release.

[0138] Furthermore a pharmaceutical composition of the invention may comprise a filler. Fillers of the present invention are pharmacologically inert and optionally nutritionally beneficial to humans and animals. Such fillers include cellulose such as microcrystalline cellulose, grain starches such as cornstarch, tapioca, dextrin, sugars and sugar alcohols such as sucrose, sorbitol, xylitol, mannitol and the like. Preferred fillers include non-fat milk powder, whey, grain brans such as oat bran, and fruit and vegetable pulps. Preferred fillers are finely divided and have a preferred average particle size in the range of about 0.10 to about 500 microns. The fillers are present in the drug delivery device in a concentration of about 50 to 80%. Optionally, the pharmaceutical particles can also serve as filler in the delivery system. Optionally, the filler may

include sterols, particularly phytosterols. (See Example 2 for use of microcrystalline cellulose for making a solid dosage form of the present invention).

[0139] In one embodiment of the invention the therapeutic agent is microencapsulated. Such microencapsulation includes sustained release encapsulation. Any known method of encapsulation is suitable in the present invention. Such methods include, but are not limited to air coating, chemical erosion, coacervation, fluid bed coating, macroencapsulation, microencapsulation, osmosis, pan spray coating, physical erosion, polymer protein conjugate systems, and polymeric microspheres. A preferred method involves slowly blending the drug with a filming agent solution to form granulated particles. The granulated particles are allowed to dry on a tray and are sieved to the desired size, typically in the range of from about 200 to about 500 microns. The coating materials include, but are not limited to, acrylic polymers and copolymers, alginates, calcium stearate, cellulose, including methylcellulose, ethylcellulose, and hydroxypropyl cellulose, gelatins, glyceryl behenate, glycolic acid and its various forms, ion exchange resins, lactic acid and its various forms, lipids, methacrylic monomers, methacrylic polymers and co-polymers, polyethylene glycol polymers, shellac (pharmaceutical glaze), stearic acid, glycerol esters of fatty acids and waxes. It is contemplated in the present invention that the microencapsulated testosterone and/or testosterone ester may be used alone, or in the lipid suspension. Further, the microencapsulated testosterone and/or testosterone ester may be used in any other system, such as tablets, boluses, enclosed in a gelatin capsule, or in a liquid or syrup system.

[0140] In another embodiment of the present invention, the therapeutic agent is not microencapsulated, but suspended in the lipid as dry particles. Where the therapeutic agent is a testosterone and/or testosterone ester, typically the testosterone and/or testosterone ester is present in the delivery device in a concentration of 50% or less. However, the testosterone can comprise all of the dried particles, to provide the necessary dose.

[0141] Optionally, the dry particles include flavorings that make the device taste and smell appealing to humans or animals. The flavorings can be natural or synthetic, and can include fruit flavorings, citrus, meat, chocolate, vanilla, fish, butter, milk, cream, egg or cheese. The flavorings are typically present in the device in the range of about 0.05 to about 1.0%.

[0142] The delivery device may also include other pharmaceutically acceptable agents, such as sweetening agents, including hydrogenated starch hydrolysates, synthetic sweeteners such as sorbitol, xylitol, saccharin salts, L-aspartyl-L-phenylalanine methyl ester, as well as coloring agents, other binding agents, lubricants, such as calcium stearate, stearic acid, magnesium stearate, antioxidants such as butylated hydroxy toluene, antifoaming agents such as dimethylsiloxane and the like.

[0143] Optionally, rupturing agents are used to rapidly deliver the testosterone and/or testosterone ester into the recipient's system. A typical rupturing agent is a starch that swells in the presence of water. Various modified starches, such as carboxymethyl starch, currently marketed under the trade name Explotab or Primojel are used as rupturing agents. A preferred rupturing agent is sodium starch glycolate. When ingested, the capsule or pellet swells in the presence of gastric juices and ruptures.

[0144] In one embodiment of the present invention, the rupturing agent is present with the therapeutic agent inside the microcapsule. As water penetrates the microcapsule, it swells the starch and ruptures the capsule, rapidly delivering the testosterone undecanoate to the system. Additional rupturing agents are disclosed in U.S. Pat. No. 5,567,439, which is hereby incorporated by reference.

[0145] In another embodiment, the rupturing agent is present in the lipid suspension, which ruptures the pellet, but leaves the microcapsules intact. This allows delayed delivery of the drug farther along in the digestive system, or in the intestines. The present invention is particularly effective in this embodiment, in that the ingested pellet may be chewable, where the pellet cleaves in the lipid suspension when chewed, but leaves the microcapsules intact. Tablets or gel capsules, when chewed, typically result in damage to or rupturing of the microcapsules defeating the effectiveness of the microcapsules.

[0146] In yet another embodiment, multiple drugs have multiple encapsulations, each containing a rupturing agent. The filming agents used for encapsulation are selected to disintegrate at selected pH conditions, which rupture and release each drug at desired locations in the digestive system.

[0147] The formulations of the present invention are prepared by conventional methods well known to those skilled in the art. The formulation can be prepared by mixing the active agent, the solubilizer, and optional additive according to methods well known in the art. Excess solvent or solubilizer, added to facilitate solubilization of the active agent and/or mixing of the formulation components, can be removed before administration of the pharmaceutical dosage form. The compositions can be further processed according to conventional processes known to those skilled in the art, such as lyophilization, encapsulation, compression, melting, extrusion, balling, drying, chilling, molding, spraying, spray congealing, coating, comminution, mixing, homogenization, sonication, cryopelletization, spheronization and granulation to produce the desired dosage form.

[0148] For dosage forms substantially free of water, i.e., when the composition is provided in a pre-concentrated form for administration or for later dispersion in an aqueous system, the composition is prepared by simple mixing of the components to form a pre-concentrate. The compositions comprising solubilized TU can be further formulated into desirable dosage forms utilizing skills well known in the art. For example, compositions in liquid or semi-solid form can be filled into soft gelatin capsules using appropriate filling machines. Alternatively, the composition can also be sprayed, granulated or coated onto a substrate to become a powder, granule or bead that can be further encapsulated or tableted or molded if the compositions solidify at room temperature with or without the addition of appropriate solidifying or binding agents. This approach allows for the creation of a "fused mixture," a "solid solution" or a "eutectic mixture."

[0149] For example, testosterone undecanoate and phytosterols form a eutectic mixture when the ratio of TU:phytosterols is 80:20. The melting point of the eutectic is 54° C. while the melting points of TU and phytosterols are 60° C. and 137° C., respectively. The dissolution profile of the eutectic is shown in FIG. 2.

[0150] FIG. 2 provides the dissolution profiles of each of Formulations 9, 51, 53, and 55, as set forth in Tables 2 and 20 herein and Capsules 2 and 4 from Example 1 of US2010/0173882. The data were obtained in a dissolution medium

incorporating 2% TritonX-100 as a surfactant in the USP 2 apparatus in accordance with the present invention. The dissolution profiles of formulations in the present invention are clearly different from those in US2010/0173882. Formulations **51**, **53** and **55** were used in the human clinical study described in Example 8.

[0151] Not previously identified is an effect observed in FIG. 4 depicting the dissolution profile of a formulation saturated with phytosterols (Formulation **59**) and one in which excess phytosterols have been added to form a waxy solid (Formulation **61**) that the concentration of phytosterols may be used to modulate the dissolution profile of formulations containing phytosterols. The dissolution profiles of FIGS. 2 and 4 illustrate that at higher concentrations phytosterols function to retard the dissolution of the therapeutic agent (FIG. 4).

[0152] FIG. 4 provides dissolution curves of TU from formulations **59**, **60**, and **61** (Table 22). Dissolution was measured in 900 mL of 25 mM phosphate buffer at pH 7.0 containing 0.1% SLS, obtained at 200 rpm using USP 2 apparatus. Formulation **59** illustrates the dissolution of a formulation with the properties of remaining a liquid a room temperature, while Formulation **60** is a suitable formulation which is solid at room temperature. Phytosterols in excess of the amount soluble at 70° C. may be added to the composition to modulate the release rate, as illustrated by the dissolution profile of Formulation **61** in FIG. 4. Formulation **61** further has the desirable property of being a sufficiently hard material that it may be reduced to a powder, which is fillable into a capsule by ordinary means.

[0153] As previously indicated, the compositions may include additional amounts of T or TU over the amount that is solubilized in the composition. In such a case, TU can be partially suspended in the composition. Such partially solubilized and partially suspended TU compositions can be prepared by adding solids of T or TU of desired form and particle size. For example, micronized crystalline T or TU having an average particle size of less than 30 microns, nanosized crystalline T or TU having an average particle size of less than 1 micron or amorphous T or TU may be added to the composition. Such micronized or nanosized T and TU particles can be obtained by precipitation or size reduction techniques well-known in the art. In addition, partially suspended T and/or TU compositions may be obtained from a supersaturated T or TU solution or by co-precipitation with an additive from a T and/or TU solution.

[0154] It is particularly preferred that an orally administered drug delivery system be prepared by first embedding the therapeutic agent(s) into phytosterols and/or phytosterol esters and an organic polymer, separately or together, in a solid state as obtained by suspension or use of a spray-drying process.

[0155] It is especially preferred to mix the testosterone products with other auxiliary agents, binders, fillers, lubricants, surfactants or disintegration accelerators and to compress or mold the mixture into tablets or fill into a capsule.

[0156] When testosterone and testosterone esters are employed along with phytosterols and/or phytosterol esters, the use of the embedding technique of spray-drying in organic polymers (polyvinylpyrrolidone, hydroxypropylmethylcellulose and its derivatives, solid polyethylene glycols), the solubility of the testosterone and testosterone esters in the intestinal fluids is enhanced.

[0157] In one embodiment, a formulation of the invention is made by dissolving testosterone and/or the particular testosterone ester, phytosterols and/or phytosterol esters together with the polymer (for example polyvinylpyrrolidone or hydroxypropyl-methylcellulose and its derivatives) in ethanol and processing the mixtures further in a spray-drying unit to form an amorphous, embedded, spray-dried formulation. It is possible in this case 1) to embed said active ingredients separately from each other or 2) to embed them together in a single processing step, to obtain an amorphous mixture.

[0158] In another embodiment, a formulation of the invention is made by suspending crystalline or amorphous testosterone and/or the particular testosterone ester, phytosterols and/or phytosterol esters in a lipid based formulation containing one or more surfactants resulting in SEDDS or SMEDDS.

[0159] The fine-particle embedded spray-dried material or the SEDDS or the SMEDDS is then subjected to dry mixing with other auxiliary agents for making tablets or capsules. The mixture is then compressed into tablets or filled into capsules.

[0160] In order to obtain a formulation with the desired release patterns, it is advantageous to individually consider characteristics of the individual components of the formulation, such as dosage of the active ingredient, ratio of testosterone to testosterone esters, selection of the ester or of the chain length at C-17 position of the androgen moiety, level of phytosterols and/or phytosterol esters, length of fatty acid chain and unsaturation level of lipids, level of surfactants, and level of sustained release polymer.

[0161] An exemplary optimized formulation is a short-acting testosterone with testosterone undecanoate (eleven-carbon chain) which has a longer half-life.

[0162] By skillful combination of testosterone with testosterone esters, in an immediate release and sustained release formulation, it is possible to attain blood level patterns which are capable of recreating or simulating the body's own rhythmicity of endogenous testosterone levels.

[0163] The present inventor has shown that by the administration of testosterone and/or testosterone undecanoate and phytosterol and/or phytosterol esters, it is possible to increase lymphatic absorption of testosterone undecanoate and modulate levels of T and DHT (FIG. 10). In selecting the testosterone ester, the choice can be made specifically from three groups: 1) esters of shorter chain length (for example, testosterone acetate or propionate), 2) esters of medium chain length (for example testosterone enanthate, cypionate or cyclohexanecarboxylate) and 3) esters of higher chain length (for example testosterone undecanoate, bucylate or palmitate).

[0164] In another embodiment, the process for preparing the composition including the formulation in a delivery system containing a lipid comprises melting the lipid, phytosterols and/or phytosterol esters and mixing with the surfactant. The dry particles of the active substance are mixed with the melted lipid/phytosterol mixture to form a suspension exhibiting pseudoplastic and/or thixotropic flow properties, and poured or molded to provide solid dosage forms (FIG. 1).

[0165] The dry particles, which include the testosterone and/or testosterone ester, filler and optional flavorings and additives, are pre-blended and typically have a particle size in the range of from about 50 microns to about 250 microns. The pre-blended particles are gradually added to the heated lipid base containing phytosterols and/or phytosterol esters until a

high solids suspension is obtained, typically in the range of about 50% to about 80% particles and from about 50% to about 20% lipid.

[0166] Slow addition of the dry particles is critical in the production of the device, to ensure that the particles are suspended in their micronized state and not as agglomerated clumps. Moreover, rapid addition can cause the mixing process to fail in that the melted suspension will not have the desired flow properties, but instead will be a granular oily mass (a sign of product failure). The mixing step is accomplished in a heated mixing device that insures thorough mixing of all materials with minimal shear, such as a planetary mixer or a scrape surface mixer. After the suspension is formed, the product is poured into molds and allowed to cool. De-molding and packaging are then performed. Alternatively, the suspension can be super-cooled and sheeted in a semi-soft format. The sheet is processed through forming rolls containing a design or configuration that embosses and forms the final shape.

[0167] The formulations and pharmaceutical compositions of the invention are useful in methods of treatment of subjects in need of such treatment. For example, the testosterone-containing formulations and pharmaceutical compositions described herein can be administered to patients who would benefit from testosterone replacement therapy. Patients suffering from any condition, disease or disorder which can be effectively treated with testosterone can benefit from the administration of a therapeutically effective amount of the testosterone-containing compositions described herein. In particular, however, the testosterone-containing compositions are effective in treating individuals suffering from androgen deficiency (e.g., postmenopausal women, menopausal women, sexually dysfunctional women, andropausal men, hypogonadal men, erectile dysfunctional men and the like).

[0168] In one embodiment the invention provides a method of treating a condition comprising administering: a) at least one lipophilic, poorly water soluble therapeutic agent; b) a phytosterol or phytosterol ester; c) a non-sterol solubilizing agent effective for solubilization of the at least one therapeutic agent; and d) an enhancing agent effective to enhance the biological absorption and/or metabolic stability of the at least one therapeutic agent. In a particular embodiment, the therapeutic agent is an androgen, and in a more particular embodiment, the androgen is selected from testosterone and testosterone esters, such as testosterone undecanoate. In a preferred embodiment the sterol or ester thereof is a phytosterol.

[0169] In a particular embodiment the invention provides a method of treating a subject in need of treatment for erectile dysfunction wherein the method comprises administration of two therapeutic agents, a first therapeutic agent comprising an androgen and a second therapeutic agent comprising a PDE V inhibitor, including, but not limited to, tadalafil (Cialis®), sildenafil (Viagra®), and vardenafil (Levitra®).

[0170] In order to characterize the absorption and bioavailability of the formulations of the present invention, animal models can be used. As noted above, Shackelford et al studied testosterone exposure in dogs dosed with testosterone undecanoate (Shackelford et al., *J. Pharmacol. And Exptl. Therap.*, 2003, vol. 306, no. 3, pp. 925-933.) and demonstrated that TU is almost exclusively absorbed through intestinal lymphatics by-passing the liver. Canine models are gen-

erally accepted in the art as predictive of human efficacy with respect to oral administration of testosterone and its esters.

[0171] Formulations of the present invention were tested in canine models, as described in Examples 4 and 5 below, which demonstrates improved TU absorption when co-dosed with phytosterols, as compared to TU dosed from a reference formulation composition similar to that of Andriol® Testocaps® (Table 23 and 24).

[0172] The inventor has found that phytosterols have unexpectedly enhanced the solubility of testosterone and/or testosterone esters in a range of lipid-based formulations from simple one lipid solubilizer component to complex 3-5 lipid solubilizer and surfactant SEDDS and/or SMEDDS formulations from about 1% to about 40% (Tables 1-20). The formulations have been divided into various classes I through VII depending on the complexity of the formulation. These tables also provide the compositions of representative formulations of the invention along with method of making them. The solubility of testosterone undecanoate in selected fatty acids, triglycerides, mono- and diglycerides, surfactants, emulsifiers, antioxidants and co-solvents were measured to select excipients for preparing representative examples of formulation(s) for each class (Table 1). The clinical formulation was also prepared with different sterols: Phytosterols, Cholesterol, Beta-sitosterol, Sitostanol (Table 19). It was unexpectedly discovered that testosterone and testosterone undecanoate enhance each other's solubility when saturated with phytosterols (Tables 16-18).

[0173] Dosage regimens and daily dosages for testosterone can vary, as a number of factors are involved, including the age and general condition of the patient.

[0174] The present invention relates to a method of administering a combination of testosterone and/or testosterone esters, phytosterols and/or phytosterol esters, mono and polyunsaturated oils and/or esters of mono and polyunsaturated oils and/or mono and polyunsaturated fatty acids in an oral preparation so that, by finely adjusted dosing of the active ingredients with improved sustained release properties, various desired plasma levels of testosterone can be set or produced in individual patients, for example to restore an endogenous body rhythm. The testosterone, when delivered in the present invention, may provide improved sustained release properties with an improvement of 10-300% over that shown in the art using micronized/nanomilled testosterone alone or testosterone undecanoate in a commercial formulation (Andriol® Testocaps®). In the delivery system, the testosterone and testosterone esters may be delivered as a solid (capsule or tablet), liquid lipid solution, or liquid lipid suspension.

[0175] In another embodiment, the invention provides a method of administering a combination of testosterone and testosterone esters (or solely testosterone esters), phytosterols and/or phytosterol esters, mono and polyunsaturated oils and/or esters of mono and polyunsaturated oils and/or mono and polyunsaturated fatty acids in an oral preparation so that, by finely adjusted dosing of the active ingredients with immediate and/or modified release properties and targeted delivery in various regions of the GI tract, various desired plasma levels of testosterone can be set or produced in individual patients along with maintaining or controlling normal physiological levels of DHT.

[0176] DHT levels in eugonadal men are typically about $1/10^{th}$ that of testosterone (i.e. about 30-110 ng/dL). Modified release dosage forms include but are not limited to those where drug release is modulated by gastric retention, muco-

adhesion, time, pH, enzymes, or pressure. In this context, improved modified release properties are adjustment of release so that the amount of DHT relative to testosterone is minimized. Testosterone interacts with receptive androgen receptors either directly or following its conversion to DHT via the action of 5- α -reductase. DHT is a more potent androgen than testosterone and elevated DHT levels are thought by some scientists to increase the risk of benign prostatic hyperplasia (BPH) and prostate cancer. Elevated levels of DHT are a noted problem with the oral or transdermal administration of testosterone and/or testosterone esters.

[0177] Pharmaceutical administration of inhibitors of 5- α -reductase enzymes is commonly used to treat benign prostatic hyperplasia (BPH) and is also used for treatment or prophylaxis of prostate cancer. Administration of 5- α -reductase inhibitors significantly reduces DHT levels within the prostate and this reduction is associated with improved outcomes for BPH and prophylaxis of prostate cancer. (McConnell, J. D. *N Engl J Med* 557-563 (1998); Roehrborn, C. G. *Urology* 434-441 (2002); Marks, L. S. *Urology*, 574-580 (1999); Debruyne, F., *Eur Urol* 488-495 (2004); Andriole, G., *N Engl J Med* 1192-202 (2010); Walsh, P. C., *N Engl J Med* 1237-1238 (2010)). However, systemic DHT, as measured by serum levels of DHT, is also reduced significantly, and this may cause undesirable side effects such as loss of muscle strength, loss of libido, erectile dysfunction, ejaculatory dysfunction, development of breast tissue, depression, acne, muscle weakness, prostatic hyperplasia, male pattern baldness, and the like in a subset of patients (Traish, A. M., *J Sex Med*, 872-884 (2011)).

[0178] These undesirable side effects are a result of the suppression of DHT levels in the whole body, while the desirable effects of 5- α -reductase inhibitor therapy are due to suppression of DHT in the prostate. It was therefore desirable to develop a method that modulates the side effect profile of treatment of DHT-related conditions by administration of a 5- α -reductase inhibitor. Such method provides desirable effects at a corporeal locus, e.g., the prostate, while avoiding the undesirable side effects on a systemic level.

[0179] While co-administration of 5- α -reductase inhibitors, such as dutasteride or finasteride, with testosterone for the purpose of androgen replacement therapy has been shown to cause DHT levels into the normal physiological range (Amory J. K., *JECM* 2610-2617 (2005)), oral dosing of testosterone is not practical for a variety of reasons: short half life, high first pass metabolism that may lead to induction and decreased testosterone levels, and the high and frequent doses required to maintain physiological testosterone levels.

[0180] The present inventors observed that when 5- α -reductase inhibitors finasteride and dutasteride are first dosed for 3 days in dogs to completely inhibit the 5- α -reductase enzyme known to reduce testosterone to DHT, followed by co-dosing with TU and finasteride or dutasteride, there was no significant change in the testosterone or DHT levels. This is contrary to published reports and patents issued claiming that finasteride and dutasteride inhibit conversion of testosterone esters to DHT (Amory J. K., *JECM* 2610-2617 (2005); Amory et al., *J Androl*, 72-78, 2006; U.S. Pat. No. 7,138,389; U.S. Patent Application No. 2008/0317844).

[0181] U.S. Patent Application Publication No. 2011/0160168, to which priority is claimed and which is incorporated by reference herein, demonstrated the enhanced modulation of solubility, stability, absorption, metabolism and/or pharmacokinetic profile of testosterone esters, in particular

testosterone undecanoate, by formulation with sterols or sterol esters where the formulations are useful in androgen replacement therapies.

[0182] Hubler et al. US 2007/0078091 described androgen replacement therapy where the androgen was supplemented with an agent that prevented prostate growth. The example provided in the application demonstrated reduced prostate growth in mice, where the treatment was a combination of testosterone and a gestagen.

[0183] U.S. Pat. No. 7,138,389 described androgen replacement therapy with co-administration of testosterone or a testosterone ester and a 5- α -reductase inhibitor, where the 5- α -reductase inhibitor was added to increase testosterone bioavailability from the administered testosterone or testosterone ester. It was concluded that testosterone and testosterone esters behave similarly with regard to co-administration of with 5- α -reductase inhibitors, i.e., that the bioavailability of the testosterone is increased and that the serum DHT levels are decreased, as compared to administration without a 5- α -reductase inhibitors.

[0184] However, later work by one of the inventors of U.S. Pat. No. 7,138,389 demonstrated that co-administration of the 5- α -reductase inhibitor finasteride with TU had no effect on either serum testosterone or serum DHT, contrary to the initial hypothesis that finasteride would increase serum testosterone and lower DHT. This lack of effect was seen with TU alone, and TU with varying amounts of finasteride (0.5 mg and 1.0 mg). It was theorized that this unexpected result was due to the lymphatic route of absorption for TU. (Roth M. Y., *Int J. of Andrology*, 1-7 (2010)).

[0185] TU is absorbed almost exclusively via the intestinal lymphatics (Coert et al., *Acta Endocrinol* (Copenh), 789-800, 1975; Nieschlag et al., *Acta Endocrinol* (Copenh), 366-374, 1975; Horst et al., *Klin Wochenschr*, 875-879, 1976; Shackelford J. *Pharmacol. and Exp. Ther.*, 925-933, 2003), thereby bypassing hepatic metabolism. For reasons of the dependence on lymphatic absorption, oral TU must be ingested with a meal containing some fat to allow for its optimal absorption and the attainment of serum testosterone concentrations within the normal range of adult men (Houwing et al., *Pharmacotherapy*, 1257-1265, 2003; Schnabel et al., *Clin Endocrinol*, 579-585, 2007). Once TU is absorbed into the intestinal lymphatics, a portion of TU is acted upon by 5- α -reductase to form dihydrotestosterone undecanoate (DHTU) (Horst et al., *Klin Wochenschr*, 875-879, 1976). After the TU and DHTU are released into circulation, non-specific plasma esterases enzymatically cleave the undecanoate ester resulting in the liberation of testosterone and DHT in the serum (FIGS. 7 and 8). The dog study demonstrates that the pharmacokinetics of orally dosed TU is not improved by the concomitant administration of the 5- α -reductase inhibitor finasteride or dutasteride. This finding is in sharp contrast to published work demonstrating that the concomitant administration of either finasteride or dutasteride significantly increased serum testosterone concentrations and significantly suppressed serum DHT concentrations when used in combination with oral testosterone in oil (Amory & Bremner, *J Clin Endocrinol Metab*, 2610-2617, 2005; Amory et al., *J Androl*, 72-78, 2006).

[0186] It therefore appears that oral TU is absorbed via intestinal lymphatics (Coert et al., *Acta Endocrinol* (Copenh), 789-800, 1975; Nieschlag et al., *Acta Endocrinol* (Copenh), 366-374, 1975), whereas the oral formulations of non-esterified testosterone are absorbed via the portal circulation

(Amory & Bremner, *J Clin Endocrinol Metab*, 2610-2617, 2005). Finasteride and dutasteride are also absorbed via the portal circulation (Carlin et al., *Drug Metabol Dispos*, 148-155, 1992; Branson et al., *J. pharmacol & Exp Ther*, 1496-1502, 1997), and their absorption is not thought to be affected by food (Steiner et al., *Clin Pharmacokinet*, 16-27, 1996).

[0187] Therefore, it is believed that finasteride and dutasteride may not be able to prevent the 5- α -reduction of the oral TU because of the different routes of absorption and such reduction results in the appearance of DHT as DHTU in the systemic circulation. Consistent with this hypothesis is the work of Horst et al., *Klin Wochenschr*, 875-879 (1976), which demonstrated the presence of significant amounts of DHTU in the thoracic ducts of men dosed orally with TU while their thoracic ducts were cannulated during neck surgery.

[0188] Contrary to the conclusion of many publications prior to Roth et al., while the conversion of testosterone to DHT is inhibited by the co-administration of 5- α -reductase inhibitors, conversion of testosterone undecanoate to DHT is not affected by the systemic inhibition of 5- α -reductase enzymes.

[0189] Accordingly, the side effects of a therapy comprising administration of a 5- α -reductase inhibitor can be modulated by administration of TU to maintain or restore normal physiological levels of DHT in tissues other than the prostate, while intra-prostatic DHT is suppressed by the 5- α -reductase inhibitor. This will minimize, alleviate and/or block many undesirable side-effects of 5- α -reductase inhibitor therapy.

[0190] In one embodiment the invention provides a method of maintaining or controlling physiological levels of DHT in a subject in need of testosterone replacement such that the physiological levels of DHT are normal or near normal and sub-physiological levels of DHT are avoided by such control or maintenance.

[0191] In a particular embodiment the method for maintaining or controlling physiological levels of DHT in a subject in need of 5-alpha reductase inhibitor therapy comprises administration of 1) testosterone undecanoate, 2) a sterol or ester thereof; 3) a non-sterol solubilizing agent effective for solubilization of the TU; and 4) an agent for enhancing the biological absorption and/or metabolic stability of the TU. In a preferred embodiment the sterol or ester thereof is a phytosterol. In a further preferred embodiment, the method results in total serum testosterone in the subject in the range of from about 300 to about 1100 ng/dL and total serum DHT in the subject in the range of from about 30 to 300 ng/dL, where the subject is a male subject. In an additionally preferred embodiment, the further embodiment the method results in total serum testosterone in the subject in the range of from about 30 to about 110 ng/dL, where the subject is a female subject.

[0192] In another embodiment the invention relates to administration of testosterone undecanoate (TU) in combination with a 5- α -reductase inhibitor to maintain or restore systemic DHT levels, while reduction of inter-prostatic DHT still occurs. By contrast, co-administration of testosterone with 5- α -reductase inhibitors does not maintain or restore systemic DHT levels (Amory, J. K. *JECM*, 2610-2617 (2005)).

[0193] The invention therefore provides a method of maintaining or restoring a DHT level in systemic circulation of an individual undergoing 5- α -reductase inhibitor therapy, the method comprising administration of a testosterone ester in addition to the 5- α -reductase inhibitor. In a particular

embodiment the testosterone ester is testosterone undecanoate. In one embodiment the 5- α -reductase inhibitor is selected from dutasteride and finasteride.

[0194] The methods of the invention, in one embodiment, provide the ability to maintain the DHT in the systemic circulation of an individual in a normal range. A normal male physiological range, as described herein, refers to a mean or average range from a group of eugonadal males. The group of individuals should be of the same gender and comparable age and weight to the individual in need of 5-alpha reductase therapy. In one embodiment the methods of the invention are effective to maintain or restore DHT levels in an individual to 30 to 300 ng/dL.

[0195] The methods of the invention include administration of a 5- α -reductase inhibitor and a testosterone ester by various routes of administration, preferably orally, but including intra-muscular injections. The methods of the invention, in various embodiments provide effective formulations for oral, parenteral, intramuscular, transdermal, nasal, sublingual, buccal and/or subcutaneous administration of a 5- α -reductase inhibitor and a testosterone ester.

[0196] "Administration" or "co-administration" of a 5- α -reductase inhibitor and a testosterone ester in methods of the invention refers to an administration in a manner that permits simultaneous or overlapping activity within the individual to which they are administered. Administration may include both of a 5- α -reductase inhibitor and a testosterone ester within a single formulation or may include a 5- α -reductase inhibitor and a testosterone ester in one or more formulations. The formulations may be administered simultaneously or may be administered separately. Administration of a 5- α -reductase inhibitor and a testosterone ester, as used herein, includes any method, formulation or composition that results in the desired serum concentration of DHT, while also maintaining desired localized DHT levels.

[0197] Example 5 demonstrates that co-administration of TU with either of the 5- α -reductase inhibitors dutasteride or finasteride results in systemic DHT levels similar to those seen in the absence of the 5- α -reductase inhibitors. This also demonstrates use of methods of the invention to provide systemic DHT levels in the normal range despite repeat dosing of dutasteride or finasteride. This is in contrast to the known and highly significant reduction in systemic DHT seen when dutasteride or finasteride is dosed alone.

[0198] Example 9 provides a rat study demonstrating decrease in prostate weight following administration of a combination of TU and dutasteride. In this study, TU alone showed normal prostate weight. This demonstrates that the methods of the invention provide effective inhibition of intra-prostatic 5-alpha reductase enzymes. Example 5 demonstrates methods to achieve normal systemic DHT levels when TU and dutasteride, or TU and finasteride, are co-administered.

[0199] In a further embodiment the invention provides a method of modulating one or more side effects of 5- α -reductase inhibitor therapy including administration of a testosterone ester in addition to the 5- α -reductase inhibitor, where administration of the testosterone ester is effective to modulate one or more side effects of the 5- α -reductase inhibitor administration. In a particular embodiment the testosterone ester is testosterone undecanoate. In a further embodiment the 5- α -reductase inhibitor is selected from dutasteride and finasteride.

[0200] Modulation of side effects of 5- α -reductase inhibitor therapy includes decreasing or eliminating one or more side effects resulting from 5- α -reductase inhibitor administration. 5- α -reductase inhibitor therapy is often associated with side effects such as testicular sensitivity, diminishment of libido, erectile dysfunction, acne, increased dermal oil production, hair loss, alopecia, decreased sperm production, decreased ejaculatory function, gynecomastia, sarcopenia, and decrease in muscle mass. Furthermore, side effects of 5- α -reductase inhibitor therapy may include diminishment in size, weight and/or volume of organs in the body, such as the prostate, seminal vesicles, and testes.

[0201] Example 9 includes Table 32, showing the results of the effects in rats on various organs by administration of TU alone and TU in combination with dutasteride. Dutasteride alone has been observed to decrease prostate and seminal vesicle weights. In Table 32 it is seen that in combination of TU and dutasteride, the dutasteride is inhibiting 5- α -reductase in the prostate but that the seminal vesicle weight and the testis weights reported are significantly higher than weights reported with dutasteride only. (Bramson, H. N., *Journal of Pharmacology and Experimental Therapeutics*, 1496-1502, (1997).) As such, it is shown that the combination of dutasteride and testosterone undecanoate modulate the undesired effect of 5-alpha reductase inhibitors on gonad physiology. Example 9 provides the resultant organ weights following the varying treatments, but it is contemplated that the decrease of the prostate weight and the increase of the seminal vesicle weight and the testis weights are correlative to the localized decrease of DHT in the prostate, while maintaining normal DHT levels elsewhere in the body (e.g., gonads).

[0202] In a further embodiment the invention provides a method of treating or preventing a DHT-related condition, the method including administration of a testosterone ester and a 5- α -reductase inhibitor. In a particular embodiment the testosterone ester is testosterone undecanoate. In a further embodiment the 5- α -reductase inhibitor is selected from dutasteride and finasteride.

[0203] DHT-related conditions or disorders include any condition that involves abnormal activity of DHT. BPH and prostate cancer are known to include elevated DHT levels in the prostate. The method of administration of testosterone undecanoate in addition to the 5- α -reductase inhibitor provides localized reduction of the DHT level in the prostate, while maintaining systemic DHT levels. In one embodiment the DHT condition is a DHT deficiency resulting from treatment for prostate cancer and the administration of testosterone undecanoate in addition to the 5- α -reductase inhibitor provides normalizing systemic DHT levels in individuals treated for prostate cancer.

[0204] The 5- α -reductase inhibitors of the methods of the invention may be administered in any amount effective to achieve the desired result. Where the 5- α -reductase inhibitors are administered as therapeutic agents for reduction of DHT, the treatment does may be in any amount effective to obtain the desired reduction of DHT. In one embodiment the 5- α -reductase inhibitor is finasteride administered in an amount from about 0.1 mg to about 400 mg, preferably about 0.5 mg to about 70 mg, more preferably about 1 mg to about 5 mg. In another embodiment the 5- α -reductase inhibitor is dutasteride administered in an amount from about 0.1 mg to about 40 mg, preferably about 0.5 to about 1 mg.

[0205] The testosterone and/or testosterone esters, when delivered, may provide total serum testosterone or dihydrotestosterone in the desired range for a period of eight (8) to twelve (12) or more hours. In one embodiment, the total serum testosterone or dihydrotestosterone is maintained in the desired range for up to about 24 hours.

[0206] Preferably, the sterol and/or sterol esters, essential fatty acids, essential fatty acid oils, and essential fatty acid esters and therapeutic agent exert an additive or synergistic therapeutic effect or the sterols mediate negative side effects of the therapeutic agent.

[0207] The formulations and pharmaceutical compositions of the invention are further useful in methods of treatment of additional hormone deficiencies and associated effects.

[0208] Accordingly the invention provides a method of treating an androgen deficiency in a subject, where the method includes administering a pharmaceutical composition of the invention.

[0209] In various embodiments the invention provides formulations and methods including biological absorption of one or more therapeutic agents. The route of such absorption is determined by the therapeutic agent used, additional elements of the formulation and/or the method of administration. In various embodiments, the absorption comprises lymphatic absorption and/or portal absorption. In specific embodiments the absorption comprises lymphatic absorption of testosterone undecanoate.

[0210] In further various embodiments, the invention provides formulations and methods used in conjunction with 5- α -reductase inhibitor therapy, in which the systemic levels of DHT are maintained, while intra-prostatic levels of DHT are lowered, as desired. In a particular method, co-dosing of TU and a 5- α -reductase inhibitor is performed.

[0211] The invention, as variously described herein in respect of features, aspects and embodiments thereof, may in particular implementations be constituted as comprising, consisting, or consisting essentially of, some or all of such features, aspects and embodiments, as well as elements and components thereof being aggregated to constitute various further implementations of the invention. The invention is described herein in various embodiments, and with reference to various features and aspects of the invention. The invention contemplates such features, aspects and embodiments in various permutations and combinations, as being within the scope of the invention. The invention may therefore be specified as comprising, consisting or consisting essentially of, any of such combinations and permutations of these specific features, aspects and embodiments, or a selected one or ones thereof.

[0212] The compositions of the invention may be further specified in specific embodiments by provisos or limitations excluding specific substituents, groups, moieties or structures, in relation to various specifications and exemplifications thereof set forth herein. Thus, the invention contemplates restrictively defined compositions, e.g., a composition excluding one or more specified ingredients.

[0213] The advantages and features of the invention are further illustrated with reference to the following examples, which are not to be construed as in any way limiting the scope of the invention but rather as illustrative of various embodiments of the invention in specific applications thereof.

Example 1

Evaluation of TU Solubility with & without Sterols in Formulations of Varying Complexity

[0214] The solubility of TU in various solubilizers was determined using conventional techniques such as incrementally adding TU until the solubilizer could no longer solubilize additional material. Table 1 below lists experimentally measured solubilities of testosterone undecanoate (TU) in various excipients of interest. Formulations 1-50 below starting with simple one component to complex 4-6 components

(Classes I through VII) were then prepared representing different categories of solubilizers. The solubility of TU and/or T was enhanced by sterols (phytosterols, cholesterol, sitostanol, and beta-sitosterol) by 1-40%. The extent of enhancement is governed by the properties of solubilizers, emulsifiers, and surfactants selected to form the formulation.

[0215] The formulations listed in Tables 1 to 20 were prepared by combining the excipients, except phytosterols, in the proportions given. The formulation was then completed by saturating with phytosterols and the addition of active agent to the desired level.

TABLE 1

Testosterone undecanoate (TU) solubility in various solubilizers	
Vehicle	TU Solubility (mg/g) at 37 C.
Oleic acid	405
Linoleic acid	391
Linolenic acid	162
Ricinoleic acid	244
Caprylic acid	595
Incromega E7010 (omega-3)	247
Incromega TG7010 SR (omega-3 high purity)	225
Omega-3 ethyl esters w/antioxidant (AMRI)	261
Omega-3 ethyl esters w/o antioxidant (AMRI)	360
Crodamol IPM (isopropyl myristate)	295
Crodamol IPP (isopropyl palmitate)	215
Crodamol EO (ethyl oleate)	221
Ethyl linoleate	230
Sunflower oil	105
Safflower oil	124
Sesame oil	138
Castor oil	218
Canola oil	167
Corn oil	243
Maisine 35-1	93
Linseed oil	179
Olive oil	161
Glyceryl trioleate (Capmul GTO)	154
Rapeseed oil	123
Soybean oil	113
Acconon CO-7	59
Miglyol 812	>100*
Capmul MCM	>100*
Capmul PG-8	>100*
Propylene glycol monolaurate	>200*
Glyceryl mono and dicaprylate/caprate (Imwitor 742)	356
Glyceryl monooleate or GMO (Peceol (Gattefosse))	323
Glyceryl ricinoleate (Softigen 701)	261
Propylene glycol monocaprylate (Capryol 90, Gattefosse)	486
Labrasol	43*
Labrafil M 1944 CS	242
Labrafil M 2125 CS	257
Polyglyceryl-3-dioleate (Plurol oleique CC497)	193
Polyglyceryl-3-diisostearate (Plurol diisosterique)	173
Polyglyceryl-6-dioleate (Caprol MPGO, Abitec)	184
Span 80	289
Polysorbate 85	125
Cremonophor RH40	88*
Polysorbate 80 (Tween 80)	39*
N-methyl pyrrolidone	>500
Transcutol HP	180
dl-alpha-tocopherol	527
Phosal 50 PG (~50% Lecithin in PG, sunflower mono-diglycerides and ascorbyl palmitate)	138

*Solubility determined at 25° C.

TABLE 2

Class I: TU + Phytosterols		
Formulation #	TU %	Phytosterols %
1	5	95
2	10	90
3	20	80
4	30	70
5	40	60
6	50	50
7	60	40
8	70	30
9	80	20
10	90	10
11	95	5

TABLE 3

Class II: TU + 1 Lipid Solubilizer + Phytosterols		
Formulation #	% Composition (w/w)	
	12	13
Ω-3 Ethyl esters w antioxidant	100	
Oleic acid		100
TU solubility mg/gm	246	385
TU solubility mg/gm saturated with phytosterols	290	418
Percent change in solubility	17.9%	8.6

TABLE 4

Mono/diglyceride or Polyoxylglyceride Based		
Formulation #	% Composition (w/w)	
	14	15
GMO (Peceol)	100	—
Labrafil M 1944 CS	—	100
TU solubility mg/gm	257	242
TU solubility mg/gm saturated with phytosterols	317	275
Percent change in solubility	23.3	13.6

TABLE 5

Class III: TU + 1 Lipid Solubilizer + Surfactant + Phytosterols Triglyceride or Fatty Acid Based			
Formulation #	% Composition (w/w)		
	16	17	18
Corn oil	65		
Oleic acid		65	
Caprylic acid			65
Cremonophor RH40	11.67	11.67	11.67
Tween 80	23.33	23.33	23.33
TU solubility mg/gm	218	254	407
TU solubility mg/gm w/ phytosterols	237	354	469
Percent change in solubility	8.7%	39.4%	15.2%

TABLE 6

Mono/diglyceride Based		
Formulation #	% Composition (w/w)	
	19	20
GMO (Peceol)	65	
Capryol 90		65
Cremophor RH40	11.67	11.67
Tween 80	23.33	23.33
TU solubility mg/gm	221	272
TU w/phytosterols	233	352
Percent change in solubility	5.4%	29.4%

TABLE 7

Polyoxylglyceride Based		
Formulation #	% Composition (w/w)	
	21	
Labrafil M 2125 CS	65	
Cremophor RH40	11.67	
Tween 80	23.33	
TU solubility mg/gm	191	
TU solubility mg/gm w/ phytosterols	252	
Percent change in solubility	31.9%	

TABLE 8

Class IV: TU + 2 Lipid Solubilizers + Surfactant + Phytosterols Fatty acid based				
Table 1 Formulation #	% Composition (w/w)			
	22	23	24	25
Oleic acid	39.85	47.86		
Caprylic acid			29.07	38.20
GMO (Peceol)	25.15		35.93	
Capryol 90		17.14		26.80
Cremophor RH40	11.67	11.67	11.67	11.67
Tween 80	23.33	23.33	23.33	23.33
TU solubility mg/gm	245	264	252	328
TU solubility mg/gm s when saturated with phytosterols	258	331	309	390
Percent change in solubility	5.3	25.4	22.6	18.9

TABLE 9

Class IV: TU + 2 Lipid Solubilizers + Surfactant + Phytosterols Triglyceride based		
Formulation #	% Composition (w/w)	
	26	27
Castor oil	40	
Corn oil		40
Labrafil M 2125 CS	25	25
Cremophor RH40	11.67	11.67
Tween 80	23.33	23.33
TU solubility mg/gm	143	144

TABLE 9-continued

Class IV: TU + 2 Lipid Solubilizers + Surfactant + Phytosterols Triglyceride based		
Formulation #	% Composition (w/w)	
	26	27
TU solubility mg/gm w/ phytosterols	195	162
Percent change in solubility	36.4	12.5

TABLE 10

Class V: TU + 3 Lipid Solubilizers + Surfactant (1 Cremophor RH40: 2 Tween 80) + Lecithin + HPMC + Phytosterols		
Formulation #	% Composition (w/w)	
	28	29
Oleic acid	30.05	30.05
GMO (Peceol)	18.97	18.97
Labrafil M 2125 CS	14.71	14.71
Cremophor RH40	11.44	
Tween 80	22.87	34.31
Lecithin	0.98	0.98
HPMC	0.98	0.98
TU solubility mg/gm	263	240
TU solubility mg/gm saturated with phytosterols	277	293
Percent change in solubility	5.3	22.1

TABLE 11

Formulation #	% Composition (w/w)		
	30	31	32
Oleic acid	30.05	30.05	30.05
Capryol 90	18.97	18.97	18.97
Labrafil M 2125 CS	14.71	14.71	14.71
Cremophor RH40	11.44	34.31	
Tween 80	22.87		34.31
Lecithin	0.98	0.98	0.98
HPMC	0.98	0.98	0.98
TU solubility mg/gm	238	231	240
TU solubility mg/gm saturated with phytosterols	277	277	282
Percent change in solubility	16.4	19.9	17.5

TABLE 12

Formulation #	% Composition (w/w)	
	33	34
Caprylic acid	30.05	30.05
GMO (Peceol)	18.97	18.97
Labrafil M 2125 CS	14.71	14.71
Cremophor RH40	11.44	34.31
Tween 80	22.87	
Lecithin	0.98	0.98
HPMC	0.98	0.98

TABLE 12-continued

Formulation #	% Composition (w/w)	
	33	34
TU solubility mg/gm	328	320
TU solubility mg/gm saturated with phytosterols	354	351
Percent change in solubility	7.9	9.7

TABLE 13

Formulation #	% Composition (w/w)	
	35	36
Caprylic acid	30.05	30.05
Capryol 90	18.97	18.97
Labrafil M 2125 CS	14.71	14.71
Cremophor RH40	11.44	
Tween 80	22.87	34.31
Lecithin	0.98	0.98
HPMC	0.98	0.98
TU solubility mg/gm	301	317
TU solubility mg/gm saturated with phytosterols	319	340
Percent change in solubility	6.0	7.3

TABLE 14

Formulation #	% Composition (w/w)		
	37	38	39
Oleic acid	45.75	45.75	45.75
GMO (Peceol)	28.88	28.88	28.88
Labrafil M 2125 CS	22.39	22.39	22.39
Cremophor RH40	1		0.33
Tween 80		1	0.67
Lecithin	0.99	0.99	0.99
HPMC	0.99	0.99	0.99
TU solubility mg/gm	384	368	366
TU solubility mg/gm saturated with phytosterols	393	410	410
Percent change in solubility	2.3	11.4	12.0

TABLE 15

Formulation #	% Composition (w/w)	
	40	41
Castor oil	30.00	
Miglyol		30.00
Lauryl glycol	20.00	20.00
Labrafil M 1944 CS	15.00	15.00
Cremophor RH40	35.00	35.00
TU solubility mg/gm	115	123
TU solubility mg/gm saturated with phytosterols	143	127
Percent change in solubility	24%	3.3%

[0216] Class VI: Formulations of T and TU with and without Phytosterol Saturation

[0217] Formulations 42-45 were prepared first without phytosterols and then saturated with phytosterols. First, the added T was used to estimate the amount of solid required to produce saturation. These samples were used to determine the solubility of T in the vehicles. As soon as the T loading was known (e.g., 1 day), the same vehicles were prepared with both T and TU above saturation.

TABLE 16

Formulation #	Composition	Composition
	(% w/w) 42	(% w/w) 43
Castor oil	29.30	—
Lauroglycol	18.73	—
Labrafil M 1944 CS	13.95	13.83
Cremophor RH40	34.08	11.64
OA	—	29.80
GMO (Peceol)	—	17.99
Tween 80	—	22.80
Lecithin	0.95	0.95
HPMC	0.95	0.95
Vit E	1.99	1.99
BHA	0.05	0.05
T alone solubility mg/gm	40	38
T alone solubility mg/gm saturated with phytosterols	43	41
Percent change in solubility	7.5	7.9
T solubility mg/gm in presence of saturated TU	46	48
T solubility mg/gm in presence of saturated TU saturated with phytosterols	47	51
Percent change in solubility	2.2	6.3
TU solubility mg/gm in presence of saturated T	183	204
TU solubility mg/gm in presence of saturated T and saturated with phytosterols	205	218
Percent change in solubility	12.0	6.9

TABLE 17

Ingredient	Formulation # 44 Composition (% w/w)
Oleic acid	100
T solubility mg/gm	35
T solubility mg/gm saturated with phytosterols	54
T solubility mg/gm in presence of saturated TU	52
T solubility mg/gm in presence of saturated TU saturated with phytosterols	58
Percent change in solubility	11.5%
TU solubility mg/gm in presence of saturated T	425
TU solubility mg/gm in presence of saturated T and saturated with phytosterols	431
Percent change in solubility	1.4%

TABLE 18

Ingredients	Formulation # 45 Composition (% w/w)
Oleic acid	45.75
GMO (Peceol)	28.88
Labrafil M 2125 CS	22.39
Tween 80	1
Lecithin	0.99

TABLE 18-continued

Ingredients	Formulation # 45 Composition (% w/w)
HPMC	0.99
T solubility mg/gm	51
T solubility mg/gm saturated with phytosterols	54
T solubility mg/gm in presence of saturated TU	51
T solubility mg/gm in presence of saturated TU saturated with phytosterols	55
Percent change in solubility	7.8
TU solubility mg/gm in presence of saturated T	358
TU solubility mg/gm in presence of saturated T and saturated with phytosterols	375
Percent change in solubility	4.7

TABLE 20-continued

Clinical and animal study formulations			
RAW MATERIAL	Unit Formulation % Formulation #		
	51 (clinical) 52 (animal)*	53 (clinical) 54 (animal)*	55 (clinical)
Hypermellose 2910 (HPMC)	0.85	0.85	0.85
dl- α -Tocopherol		2.00	1.77
Butylated Hydroxyanisole (BHA)	0.05	0.05	0.05

*Formulations used for animal studies did not contain dl- α -Tocopherol or BHA.

TABLE 19

Class VII: Solubility of TU in Oleic Acid Based Formulation with Cholesterol, Stigmastanol (β -sitostanol) and β -sitosterol					
Formulation #	Composition (% w/w)				
	46	47	48	49	50
Ingredients	OA	OA	OA-Chol	OA-Stig	OA- β -sitosterol
OA	29.80	29.80	29.80	29.80	29.80
GMO (Peceol)	17.99	17.99	17.99	17.99	17.99
Labrafil M 1944 CS	13.83	13.83	13.83	13.83	13.83
Cremophor RH40	11.64	11.64	11.64	11.64	11.64
Tween 80	22.80	22.80	22.80	22.80	22.80
Sterol	No sterols	Sat. w/ phytosterol	Sat. w/ Cholesterol	Sat. w/ Stigmastanol	Sat. w/ β -sitosterol
Lecithin	0.95	0.95	0.95	0.95	0.95
HPMC	0.95	0.95	0.95	0.95	0.95
Vit E	1.99	1.99	1.99	1.99	1.99
BHA	0.95	0.05	0.05	0.05	0.05
TU solubility, mg/gm	152	155	162	160	179
Percent change in solubility compared to the 'no sterols' column	—	2.0	6.6	5.3	17.8

TABLE 20

Clinical and animal study formulations			
RAW MATERIAL	Unit Formulation % Formulation #		
	51 (clinical) 52 (animal)*	53 (clinical) 54 (animal)*	55 (clinical)
Testosterone Undecanoate	11.54	11.54	11.54
Castor oil	25.40		
Oleic acid		25.93	25.93
Lipoid E PC S (Egg Lecithin)	0.85	0.85	0.85
Cremophor RH40	29.63	9.88	9.87
Polysorbate-80		19.74	19.73
Labrafil M 1944 CS	12.70	11.69	5.17
Lauroglycol 90	16.93		
Glycerol mono-oleate Type 40		15.37	8.85
Precirol ®			13.26
Phytosterols as CardioAid XF	2.12	2.11	2.12

[0218] For those formulations where the level of phytosterols was achieved by saturation, the level of phytosterols is from about 2% to about 20%. The level of solubilizers ranges from about 10% to about 90%. The level of surfactants ranges from about 1% to about 35%.

[0219] This example shows that formulations containing TU and/or T may be prepared from the compositions of Table 1-20 to contain the active agent in any concentration up to the solubility shown. In addition, the formulation may be further modified by addition of testosterone and/or testosterone ester beyond the solubility shown, while retaining useful dissolution and other pharmaceutical properties. FIG. 4 of Example 3 illustrates this modulation of properties.

Example 2

Preparation of Compositions Comprising Testosterone Undecanoate

[0220] Compositions comprising T, TU, and Phytosterol were prepared by weighing out the components in the

described amount, placing the components into an appropriate container, mixing the components in an appropriate manner and, if necessary, heating to facilitate the solubilization of T, TU, and Phytosterols in the formulation. The formulations can be prepared by adding the components in any order. For example, T, TU, and phytosterols can be added to an individual component or into mixtures of two or more components. The composition can be prepared at room temperature or gently heated to 40-60° C. The composition can also be prepared by melting TU or Phytosterol and/or phytosterol esters at a temperature above the melting point, i.e., 64-66° C., followed by mixing it with other components. Traditional mixing techniques can be used, including, for example, mechanical agitation, stirring and sonication of the components. The clinical formulations **51**, **53**, and **55** were prepared using semi-automated equipment. A flow chart of a small-scale manufacturing process for preparation of pharmaceutical products suitable for clinical use is shown in FIG. 1. This process is suitable for the small scale manufacture of HPMC capsules, and it is a simple matter to adapt the process to gelatin capsules by replacing the HPMC banding solution with a gelatin banding solution. Other means of sealing capsules are also available, such as the LEMS™ system used with LiCaps™. Formulations containing only TU and Phytosterols were prepared by melting the mixture and cooling to room temperature. The solid was ground to a powder and filled into gelatin or HPMC capsules.

[0221] Formulations which are liquid at room temperature can be converted into free flowable powder or a waxy solid by addition of carriers or spraying the formulation on to an inert carrier. An example of preparing a solid powder is given below in Table 21. The liquid formulation was prepared by heating TU, excess phytosterols, and all other excipients at 70° C. for one day and cooled to room temp. Microcrystalline cellulose was added to absorb the formulation and yield a solid that was ground to a powder and filled in a HPMC capsule. The dissolution profile of the formulation is shown in FIG. 3.

[0222] The dissolution profiles of selected formulations prepared in the above manner and chosen from Table 2-21 are shown in FIGS. 2 and 3.

[0223] In FIG. 2, dissolution profiles are provided for all of TU formulations **51**, **53** and **55** (Table 20); Formulation **9** (Table 2), and Capsules 2 and 4 of Example 1 from US2010/0173882. The data were obtained in a dissolution medium incorporating 2% TritonX-100 as a surfactant in the USP 2 apparatus in accordance with the present invention.

[0224] In FIG. 3, dissolution profiles are provided for all of TU Formulations **17** (Table 5), **28** (Table 10), **39** (Table 14), **56**, **57** (Table 27) and **58** (Table 21). The data were obtained in a dissolution medium incorporating 2% TritonX-100 as a surfactant in the USP 2 apparatus in accordance with the present invention.

TABLE 21

Ingredient	Formulation # 58 Composition (% w/w)
TU	120 mg/gm
OA	30.05
GMO	18.97
Labrafil M 1944 CS	14.71
Cremophor RH40	11.44
Tween 80	22.87

TABLE 21-continued

Ingredient	Formulation # 58 Composition (% w/w)
Phytosterol	Saturated
Lecithin	0.98
HPMC	0.98
Microcrystalline Cellulose	40 parts of microcrystalline cellulose were added to 60 parts of the above formulation.

Example 3

Preparation of Compositions Comprising Testosterone Undecanoate and Phytosterols

[0225] The percentage of phytosterol in the phytosterol-saturated formulations ranges from 2% to 20%. Three formulations are described in Table 22 containing between 5.8% and 44.6% phytosterols. FIG. 4 describes the dissolution profiles of these three formulations. Dissolution was measured in 900 mL of 25 mM phosphate buffer at pH 7.0 containing 0.1% SLS, obtained at 200 rpm using USP 2 apparatus. Formulation **59** illustrates the dissolution of a formulation with the properties of remaining a liquid a room temperature, while Formulation **60** is a suitable formulation which is solid at room temperature. Phytosterols in excess of the amount soluble at 70° C. may be added to the composition to modulate the release rate, as illustrated by the dissolution profile of Formulation **61** in FIG. 4. Formulation **61** further has the desirable property of being a sufficiently hard material that it may be reduced to a powder, which is fillable into a capsule by ordinary means. As can be seen from FIG. 4, phytosterols behave as delayed release agents due to their high log P (~12) and hydrophobic properties.

[0226] The formulations of Table 22 range in phytosterol composition from about 6% to 45% by weight. The same formulations range in TU composition from about 20% to about 72% by weight.

TABLE 22

Component	Formulation compositions with phytosterols		
	Percent composition		
	Formulation 59	Formulation 60	Formulation 61
TU	20.3%	71.7%	42.2%
Oleic acid	18.5%	6.7%	4.0%
GMO	11.1%	4.0%	2.4%
Labrafil M 1944 CS	8.4%	3.1%	1.8%
Cremophor RH40	7.1%	2.6%	1.5%
Tween 80	14.1%	5.1%	3.0%
Phytosterols	18.2%	5.8%	44.6%
Lyso Lecithin	0.6%	0.2%	0.1%
HPMC	0.6%	0.2%	0.1%
Vitamin E	1.3%	0.5%	0.3%

Example 4

In Vivo Dosing and PK Profile of Testosterone Undecanoate in Lipid Formulations

[0227] A test was conducted of TU-containing lipid formulations for increased absorption in accordance with the methods of Shackelford et al., *J. Pharmacol. And Exptl. Therap.*, 2003, vol. 306, no. 3, pp. 925-933.

[0228] Test formulations were administered to four beagle dogs (body weight 8-10 kg) with food. The dosages were delivered as formulations consisting of two or three capsules. There were six different formulations in this study and they were identified by letters A through F.

[0229] Treatment A was a reference formulation of testosterone undecanoate (40 mg TU in a vehicle of 60:40 castor oil:lauroglycol, which is the formulation of the commercial product Andriol Testocap®). Treatments B through F all contained TU in castor oil base (Formulation 52 in Table 20) and are described in Table 23. All treatments, including the reference formulation contained a dosage of 80 mg per dog of TU, and one treatment also contained 100 mg of testosterone (T).

[0230] Whole venous blood samples of approximately 2.0 mL were collected from a peripheral vein of all animals for determination of serum concentrations of the reference or test article. Samples were collected at the following target time points at each dose: predose, 0.25, 0.5, 1, 2, 4, 6, 8 and 12 hours after administration.

[0231] Graphs of the results of serum concentration analyses for TU and T are provided in FIG. 5. It can be seen from FIG. 5 that significant TU absorption was observed with Formulation C (TU+castor oil+solubilized phytosterols+solid phytosterols), Formulation B (TU+castor oil+solubilized phytosterols) and Formulation D (TU+castor oil+solubilized phytosterols+phytosterols esters), as compared to reference Formulation A, lacking phytosterols.

[0232] The TU and T area under the curve (AUC) results and relative bioavailability were as follows:

[0233] This example demonstrates that the formulations of the present invention increase the absorption of TU up to 2-fold, as compared to a commercial formulation. The resulting T exposures are also increased.

Example 5

In Vivo Dosing and PK Profile of Testosterone Undecanoate in Lipid Formulations

[0234] This study consisted of two parts: Part 1 and Part 2. Part 1 of the study examined the effects of the metabolic inhibitors dutasteride and finasteride, and Part 2 examined the effect of 800 mg of phytosterols on T and DHT.

[0235] Part 1 consisted of two arms: a dutasteride arm and a finasteride arm. In the dutasteride arm four female Beagle dogs were dosed with 80 mg testosterone undecanoate (#52) and 400 mg phytosterol powder for three days (Days 3-5) followed by dutasteride at 2.5 mg (a one day loading dose; Day 6) and dutasteride at 0.5 mg for three more days (Days 7-9). These dogs then received 80 mg testosterone undecanoate (#52), 400 mg phytosterol powder, and 0.5 mg dutasteride for three days (days 10-12). The finasteride arm (four female Beagle dogs) was dosed identically to the dutasteride arm except finasteride at 5.0 mg was given instead of dutasteride, and the study lasted an additional three days (Days 13-15), during which 400 mg phytosterol only was dosed the first two days (Days 13, 14), and 80 mg TU in oleic acid formulation (#54) plus 400 mg phytosterols were dosed on Day 15. All testosterone undecanoate doses were administered to animals in the fed state.

[0236] Part 2 consisted of one arm and four female Beagle dogs were dosed with 80 mg testosterone undecanoate and 800 mg phytosterol powder for one day. All doses of testosterone undecanoate were administered to animals in the fed state.

[0237] Whole venous blood samples of approximately 2.0 mL were collected from a peripheral vein of all animals for determination of serum concentrations of T and DHT by LCMS. Samples were collected at the following target time points at each dose: predose, 0.25, 0.5, 1, 2, 4, 6, 8 and 12 hours after administration.

TABLE 23

PK parameters from a formulation study in beagle dogs						
Treatment description	Mean TU exposure, ng*h/mL	Standard Deviation	Relative bioavailability (TU)	Mean T exposure, ng*h/mL	Standard Deviation	Relative bioavailability (T)
A 80 mg TU in a formulation of 60:40 castor oil:lauroglycol	1029.9	349.2	100%	65.6	16	100%
B 80 mg TU as Formulation 52	1437.8	454.9	140%	83.9	21	128%
C 80 mg TU as Formulation 52, co-dosed with 400 mg phytosterols	2181.5	1124.0	212%	99.7	20.7	152%
D 80 mg TU as Formulation 52, co-dosed with 640 mg phytosterol esters	1357.5	829.6	132%	62.1	19.8	95%
E 80 mg TU as Formulation 52, 100 mg of testosterone, 640 mg phytosterol esters	1297.5	214.1	126%	143	48.1	218%
F 80 mg TU as Formulation 52, 5 mg finasteride	1700.0	867.8	165%	76.4	13.4	116%

[0238] Graphs of the results of serum concentration analyses for testosterone are provided in FIG. 6. It can be seen from FIG. 6 that significant systemic T exposure was observed with the oleic acid formulation (#54) relative to the Castor oil formulation (#52). The DHT levels with the Oleic acid formulation were also significantly lower relative to the Castor oil formulation (#52) as shown in FIG. 10.

[0239] It can be seen from Table 23 that 5- α -reductase inhibitors had no significant effect on the T and DHT exposures.

[0240] Graphs of the results of serum concentration analyses for testosterone for Part 2 evaluating the effect of 800 mg of phytosterol vs. 400 mg in Part 1 using the castor oil formulation (#52) are provided in FIG. 9. It can be seen from FIG. 9 that there was no difference in T levels with increased levels of phytosterols.

[0241] Bar graphs of average T and DHT exposures (ng-h/mL) for all six treatments of TU formulations in beagle dogs in this study are given in FIG. 10. All treatments were co-dosed with 400 mg phytosterols except treatment L which was co-dosed with 800 mg of phytosterols. Error bars represent plus and minus one standard deviation.

[0242] It can be seen from FIG. 10 that oleic acid formulation gives the highest T level and lowest DHT level of all the treatments tested. The DHT/T ratio for this formulation is approaching the normal DHT/T value of 0.17 to 0.26 (FIG. 11). The numerical data for TU and T exposure and relative bioavailabilities for this study is given in Table 24 below.

[0243] This example demonstrates that formulations of the present invention enhance TU absorption relative to the reference formulation (Treatment A of Table 23) by up to 3-fold. This example also demonstrates that resulting T exposures are increased up to 3-fold relative to the same reference formulation. It is also observed that the DHT/T ratios for Treatment K and L approach the normal physiological values in humans, versus other formulations. This example also demonstrates that co-administration of TU with either of the 5-alpha reductase inhibitors dutasteride (Treatment H) or finasteride (Treatment J) results in systemic DHT levels similar to those seen in the absence of the 5-alpha reductase inhibitors (Treatment G and I, respectively).

Example 6

Lipid Dispersion Studies

[0244] The lipid dispersion test can be used to select formulations that maximize the amount of TU in the aqueous phase.

[0245] Buffer solution (100 mL) is prepared. Each test requires 36 mL with the following composition: 50 mM TRIS maleate/150 mM NaCl/5 mM CaCl₂·2H₂O/5 mM Na taurodeoxycholate/1.25 mM lecithin.

[0246] TRIS, maleic acid, NaCl and CaCl₂·2H₂O are dissolved together. The buffer can be made to about 90% final volume, with adjustment of the pH to 6.8 with NaOH or HCl. Na taurodeoxycholate is dissolved into the solution. Lipoid E

TABLE 24

PK parameters from a formulation study in beagle dogs									
Treatment description	Mean TU exposure, ng*h/mL	Standard Deviation	Relative bioavailability TU ³	Mean T exposure, ng*h/mL	Standard Deviation, T	Relative bioavailability (T) ³	DHT/T ratio	Mean DHT exposure ng*h/mL	Standard Deviation, DHT
G ¹ : Formulation 52 80 mg TU in a castor oil formulation, co-dosed with 400 mg phytosterols	3570	1020	347%	126	16	192%	0.43	54	37
H ¹ : Formulation 52 80 mg TU in a castor oil formulation, co-dosed with 400 mg phytosterols, co-dosed with 0.5 mg dutasteride	2680	989	260%	132	28	201%	0.77	101	65
I ² : Formulation 52 80 mg TU in a castor oil formulation, co-dosed with 400 mg phytosterols	2300	1803	223%	122	19	186%	0.55	68	24
J ² : Formulation 52 80 mg TU in a castor oil formulation, co-dosed with 400 mg phytosterols, co-dosed with 5 mg finasteride	1660	342	161%	115	34	175%	0.56	64.2	5
K Formulation 54 80 mg TU in an oleic acid formulation, co-dosed with 400 mg phytosterols	3030	474	294%	210	18	320%	0.26	55	21
L: Formulation 52 80 mg TU in a castor oil formulation, co-dosed with 800 mg phytosterols	2630	969	255%	138	31	210%	0.27	37.5	31

¹Treatment G is the control arm for Treatment H

²Treatment I is the control arm for Treatment J

³Referenced to the TU and T exposures of Treatment A, Table 23.

PC S should be removed from the freezer and allowed to thaw to room temperature in its bag with desiccant before removing it from the bag. Lecithin is dissolved, which requires stirring for several hours for the solution to clarify. The solution is quantitatively transferred back into a volumetric flask and diluted to volume with purified water. The final pH is checked and recorded it on the flask. Once the solution is made, it is stored in the refrigerator.

TABLE 25

Dispersion media				
Component	MW (g/mol)	Molarity (M)	Wt (g) to make 100 mL	Wt (g) to make 500 mL
TRIS (base)	121.14	0.05	0.6057	3.0285
Maleic acid	116.08	0.05	0.5804	2.902
NaCl	58.44	0.15	0.8766	4.383
CaCl ₂ —2H ₂ O	147.02	0.005	0.07351	0.36755
Na taurodeoxycholate (hydrate)	521.7	0.005	0.26085	1.30425
Lecithin (Lipoid E PC S)	775	0.00125	0.096875	0.484375

Dispersion Experiment

[0247] Procedure: To the 36 mL of the dispersion buffer add 0.2 mL of formulation (initial test will use vehicle blank) quantitatively. Note that 0.2 mL per 40 mL is equivalent to about 1 mL in 200 mL, so it is a biorelevant amount. Draw samples every 15 minute to assess dissolution over 60 min; analyze for TU.

[0248] The results are presented in Table 26 below. The improved dispersion properties of the invention are evident in the percentage of TU solubilized. The Castor oil:lauroglycol formulation is the same composition as Andriol® Testocaps®.

TABLE 26

Results of dispersion testing of 60 mg of TU in Formulation 52 and castor oil:lauroglycol 60:40	
Formulation	TU percent contained in dispersed phase
Castor oil:lauroglycol 60:40	0%
Formulation 52	84.5%

Example 7

Stability of Compositions Comprising Testosterone Undecanoate

[0249] The following formulations were stored at 60° C. for up to 2 weeks. The Iodine values for the formulations 56 and 57 were measured at 0, 1, and 2 weeks to assess the stability of the unsaturated excipients in the formulation, in the presence and absence of phytosterols.

TABLE 27

Ingredient	Formulation #	
	56 Composition (% w/w)	57
TU	120 mg/gm	120 mg/gm
OA	30.05	30.05
GMO	18.97	18.97
Labrafil M 1944 CS	14.71	14.71
Cremophor RH40	11.44	11.44
Tween 80	22.87	22.87
Phytosterol	0	Saturated*
Lecithin	0.98	0.98
HPMC	0.98	0.98

*Component percentages are taken before saturation of the vehicle with phytosterols at 70° C.

[0250] The iodine value I_T is the number that expresses in grams the quantity of halogen, calculated as iodine, that can be fixed in the prescribed conditions by 100 g of the substance. Iodine value test per USP <401> Fats and Fixed Oils (Method 1) is used for determining the Iodine number. The method follows.

[0251] Procedure: Introduce the prescribed quantity of the substance to be examined (mg) into a 250 ml flask fitted with a ground-glass stopper and previously dried or rinsed with glacial acetic acid, and dissolve it in 15 ml of chloroform unless otherwise prescribed. Add very slowly 25.0 ml of iodine bromide solution. Close the flask and keep it in the dark for 30 min unless otherwise prescribed, shaking frequently. Add 10 ml of a 100 g/l solution of potassium iodide and 100 ml of water. Titrate with 0.1 M sodium thiosulphate, shaking vigorously until the yellow color is almost discharged. Add 5 ml of starch solution and continue the titration adding the 0.1 M sodium thiosulphate dropwise until the color is discharged (n_1 ml of 0.1 M sodium thiosulphate). Carry out a blank test under the same conditions (n_2 ml of 0.1 M sodium thiosulphate).

$$I_T = \frac{1.269(n_2 - n_1)}{m}$$

[0252] Iodine number values after 1 and 2 weeks are given in Table 28. It can be seen from Table 28 that phytosterols minimize the degradation of the oxidation of the double bonds in the lipid-based formulations. This discovery enables longer shelf-life for oxidation-prone lipid-based formulations to be achieved.

TABLE 28

Stability results Iodine Test			
Formulation	Initial	1 week at 60° C.	2 weeks at 60° C.
56	59.48	42.89	41.86
57	59.20	57.24	53.26

[0253] The clinical formulations 51, 53, and 55 the compositions of which are listed in Table 20 were stored at 25° C./60RH for 4 weeks. The TU content and impurities were measured at 0, and 4 weeks. Results at 0 and 4 weeks are given in Table 29.

TABLE 29

Stability results		
Formulation	Initial (related imps)	4 weeks at 25° C./60RH (related imps)
51	101.8% (0.23)	99.6% (0.50)
53	100.4%(0.43)	98.7%(1.11)
55	101.8%(0.45)	98.5%(0.92)

[0254] The results in Table 28 demonstrate that phytosterols enhance the stability of formulations containing unsaturated fatty acids or glycerides. Table 29 demonstrates the acceptable stability of the clinical formulations 51, 53, and 55 (Table 20).

Example 8

In-Vivo Dosing and Prediction of Human PK Parameters of Compositions Comprising Testosterone Undecanoate

[0255] Formulations 51, 53, and 55 were selected for assessment of PK profile in hypogonadal men. These capsules were manufactured according to Example 2, each capsule containing 40 mg of TU. Using accepted principles of allometric scaling and the direct comparison of the in-vivo results obtained with Andriol® Testocaps®, human clinical exposures are predicted as in Tables 30 and 31.

[0256] A randomized, single-dose, open-label, 5-period crossover study to evaluate the bioavailability, safety, and tolerability of four different testosterone undecanoate treatments versus a reference formulation (Andriol® Testocaps®) that is the current marketed formulation of TU was performed. Three investigational formulations 51, 53, and 55 comprised three of the treatments; the fourth treatment was a combination of the two (Formulations 53 and 55) of the investigational formulations. The study enrolled hypogonadal men that have low systemic testosterone levels but do not exhibit clinical symptoms at such levels (i.e., the subjects are asymptomatic).

[0257] A total of 8 subjects were enrolled to receive a single dose of each of the four test treatments (80 mg TU per dose) and the reference formulation (80 mg TU as Andriol® Testocaps®) under fed conditions in crossover fashion. Subjects were randomized to treatment sequence with a washout period of 24 hours (period 1 to 3 for Andriol® Testocaps®, formulation 51 and 53) or 48 hours (period 4 and 5 for formulations 55 and 53+55) between each blinded administration of study drug. Each dose of study drug was immediately preceded by a standard meal to allow for dosing in the fed state.

[0258] Serial blood samples for serum PK analysis of testosterone and dihydrotestosterone (DHT) levels were collected at 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 24 and additional 16 and 48 (period 4 and 5) hours after dosing of each of the test and reference TU formulations to characterize single-dose bioavailability and pharmacokinetics. Vitals signs, AEs, clinical labs, ECGs, and urinalysis was assessed pre-dose and at various times through discharge.

[0259] Based on the dog PK data on Andriol® Testocaps® and formulations 52 and 54 and available human data on Andriol® Testocaps®, the predicted human C_{avg} for formulations 51 and 53 is given in Tables 30 and 31. Note that Formulations 51 and 53 are derived from Formulations 52 and

54 by addition of minor amounts of antioxidants. For comparison, the steady state testosterone C_{avg} of a SEDDS formulation from Clarus Therapeutics with a dose of 316 mg of TU (200 mg T equivalent) is 514 ng/dL (Roth et al, International Journal of Andrology, on-line issue October 2010).

[0260] Allometric scaling was carried out using the published method contained in guidance published by the Food and Drug Administration of the United States (FDA), in Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, published in July 2005. The factor of 0.54 is used to convert from mg/kg dosing in dogs to the approximate equivalent dose in humans. In the in-vivo study in beagle dogs, the TU dose was 80 mg, the average animal weight 9.4 kg, and the dose/kg body weight is 8.5 mg/kg. The equivalent human dose is 8.5 mg/kg X 0.54=4.6 mg/kg. For a proposed human dose of 80 mg, and an average adult male weight of 60 kg, the dose/kg body weight would be 1.3 mg/kg. Assuming linear pharmacokinetics for T-exposure resulting from the dosing of TU, the resulting predicted human exposure factor for the 80 mg human dose is (1.3/4.6)=0.28.

TABLE 30

Predicted human PK parameters for testosterone for Formulations 52 and 54 by allometric scaling	
Formulation	AUC (0-12) (ng-h/mL)
Formulation 52 result in dogs	99.7
Predicted human PK parameter of Formulation 51	27.9
Formulation 54 result in dogs	210
Predicted human PK parameter of Formulation 53	58.8

[0261] A direct comparison of the T exposure (C_{max} and AUC) between dogs and humans is also possible based on published data for Andriol® Testocaps® (Bagchus et al). The resulting predicted values of the AUC (0-12 hr) exposure is somewhat higher than the allometric approach using the direct comparison approach.

TABLE 31

Predicted human PK parameters for 80 mg TU dose for Formulations 52 and 54 by direct comparison method		
Composition or formulation	C_{max} ng/mL	AUC 0-12 hrs ng-h/mL
Dog: 60:40 castor oil:lauroglycol FCC	7.7 ¹	35.6 ¹
Human: 60:40 castor oil:lauroglycol FCC	32.9 ²	65.6 ²
Ratio dog:human:	0.23	0.54
Formulation 52 result in dogs	53.6	99.7
Predicted human PK parameters of Formulation 51 ³	12.5	54.1
Formulation 54 result in dogs	123	210

TABLE 31-continued

Predicted human PK parameters for 80 mg TU dose for Formulations 52 and 54 by direct comparison method		
Composition or formulation	Cmax ng/mL	AUC 0-12 hrs ng-h/mL
Predicted human PK parameters of Formulation 53 ³	28.8	113.4

¹Treatment in beagle dogs is the same composition as published for Andriol® Testocaps® except filled into hard gelatin capsules.

²Testocaps® from Andriol® Testocaps® web site, W M Bagchus, F Maris, P G Schnabel, N S Hourwing, Dose Proportionality of Andriol® Testocaps®™)

³Phytosterols, 400 mg, co-administered with Formulations 52 and 54 to dogs. Formulations 51 and 53 will be co-administered in humans with phytosterols, 400 mg.

[0262] FIG. 12 shows the predicted average human concentrations of T and DHT resulting from dosing with Formulations 51 and 53. Treatment I is Formulation 51 co-dosed with 400 mg phytosterols. Treatment K is Formulation 53 co-dosed with 400 mg phytosterols. Treatment L is Formulation 51 co-dosed with 800 mg phytosterols. The predictions of human exposure are based on extrapolation of in vivo results in beagle dogs, using the beagle dog and human PK parameters for a reference formulation of TU in 60% castor oil and 40% lauroglycol.

Example 9

Administration of Dutasteride in Combination with TU

[0263] Male Sprague-Dawley rats were treated with one of three treatments:

[0264] Group 1: vehicle alone (Maisine 35-1/Cremophor RH40/Vitamin E/Phytosterol Esters) (“vehicle-only arm”);

[0265] Group 2: testosterone undecanoate in vehicle (“TU arm”); and

[0266] Group 3: testosterone undecanoate plus dutasteride in vehicle (“T+D arm”)

[0267] After 14 days of dosing, organ weights were obtained and are provided in Table 5 below. The organ weights obtained from Bramson et al. are given in the right-hand column of the table for reference (Bramson, H. N., *Journal of Pharmacology and Experimental Therapeutics*, 1496-1502, (1997).)

TABLE 32

Organ (weights in grams)	Group			Literature reference Bramson et. al 1 mg/kg/day D
	1 Vehicle only	2 80 mg/kg/ day TU	3 80 mg/kg/ day TU and 1 mg/kg/day D	
Body weight (g)				
Mean	282	284	280	275.3
SD	25.8	13.5	15.1	3.3
Seminal vesicles				
Mean	0.966	0.902	0.56	0.17
SD	0.2245	0.1971	0.2003	0.22
Testicles				
Mean	3.309	3.374	3.458	1.32 ¹
SD	0.37	0.2077	0.2094	0.03

TABLE 32-continued

Organ (weights in grams)	Group			Literature reference Bramson et. al 1 mg/kg/day D
	1 Vehicle only	2 80 mg/kg/ day TU	3 80 mg/kg/ day TU and 1 mg/kg/day D	
Ventral prostate				
Mean	0.25	0.22	0.14	0.12
SD	0.108	0.08	0.032	0.007

¹In Bramson et al., only the right testicle was weighed.

[0268] In the T+D arm (Group 3), decreases in the weights of the ventral prostate and seminal vesicles were statistically significant ($P < 0.05$). No significant differences in weight were observed between the vehicle-only (Group 1) and TU arm (Group 2) for any organ measured.

[0269] The decrease in ventral prostate weight demonstrates that the dutasteride is inhibiting 5- α -reductase in the prostate despite administration of testosterone in the form of testosterone undecanoate. The decreases in prostate and seminal vesicle weights are consistent with prior observations of the effect of dutasteride in rats. (Bramson, H. N., *Journal of Pharmacology and Experimental Therapeutics*, 1496-1502, (1997).)

[0270] The seminal vesicle weight and the testis weights in the TU+D arm (Group 3) are significantly higher than the D-only reference data of Bramson et al. This demonstrates that the combination of 5- α reductase inhibitor dutasteride and testosterone undecanoate modulate the undesired effect of 5- α reductase inhibitors on gonad physiology.

[0271] While the invention has been described herein in reference to specific aspects, features and illustrative embodiments of the invention, it will be appreciated that the utility of the invention is not thus limited, but rather extends to and encompasses numerous other variations, modifications and alternative embodiments, as will suggest themselves to those of ordinary skill in the field of the present invention, based on the disclosure herein. Correspondingly, the invention as hereinafter claimed is intended to be broadly construed and interpreted, as including all such variations, modifications and alternative embodiments, within its spirit and scope.

What is claimed is:

1. A method of modulating one or more side effects of 5- α -reductase inhibitor therapy, the method comprising administering:

- a) a 5- α -reductase inhibitor; and
- b) testosterone undecanoate;

wherein the administration of testosterone undecanoate is effective to modulate the one or more side effects of the 5- α -reductase inhibitor administration.

2. The method of claim 1, wherein the 5- α -reductase inhibitor is selected from dutasteride and finasteride.

3. The method of claim 1, wherein the modulating comprises decreasing the one or more side effects.

4. The method of claim 1, wherein the modulating comprises eliminating the one or more side effects.

5. The method of claim 1, wherein the one or more side effects include at least one effect selected from testicular sensitivity, diminishment of libido, erectile dysfunction, acne, increased dermal oil production, hair loss, alopecia,

decreased sperm production, decreased ejaculatory function, gynecomastia, sarcopenia, and decrease in muscle mass.

6. The method of claim 1, wherein the modulating the one or more side effects comprises a decrease in the size, volume or weight of the seminal vesicles.

7. The method of claim 1, wherein the modulating the one or more side effects comprises a decrease in the size, volume or weight of the testes.

8. A method of maintaining or restoring a serum DHT level in an individual undergoing 5- α -reductase inhibitor therapy, the method comprising administration of testosterone undecanoate in addition to the 5- α -reductase inhibitor.

9. The method of claim 8, wherein the administration of testosterone undecanoate in addition to the 5- α -reductase inhibitor is effective to achieve a serum DHT level of about 30 to about 300 ng/dL.

10. The method of claim 8, wherein the 5- α -reductase inhibitor is selected from dutasteride and finasteride.

11. A method of treating or preventing a DHT-related condition, the method comprising administering:

a) a 5- α -reductase inhibitor; and

b) testosterone undecanoate.

12. The method of claim 11, wherein the DHT-related condition is selected from benign prostatic hyperplasia (BPH), prostate cancer, and DHT deficiency from prior prostate cancer treatment.

13. The method of claim 11, where the 5- α -reductase inhibitor is selected from dutasteride and finasteride.

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